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PANEL DISCUSSION ON CLINICAL NUTRITION AND LIPID METABOLISM*

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PART I

MODERATOR LAURANCE W. KINSELL: This panel is composed of people in clinical and investigative medicine and in basic sciences related to medicine. We plan to have an informal approach in our discussion. The first part of the discussion will be devoted to a consideration of nonlipids, and the second half almost entirely to lipids. Needless to say, with two sessions extending only about one hour and a quarter each, we can cover only the highlights.

Since the food taken by all of us has a bearing upon our general health and vigor, it would seem not unreasonable to believe that the overall process of aging may be associated, either on the plus side or the minus side, with good or bad nutrition. If so, perhaps a place to begin our considerations would be at the upper end of the digestive tract. We could start with some comments about teeth, dentures, and other aspects of this part of the problem. Dr. Wilkinson, will you give us your thoughts?

DR. CHARLES F. WILKINSON, JR.: The attitude of older persons toward food,

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and their ability to taste it are quite important. Some good work has shown that the usual type of upper denture, that is, a solid plate, decreases the sensitivity of taste perception. Pusey, in the *Journal of the American Medical Association* for April 20, 1940, described an upper denture made with vitallium bars rather than a solid top. This helped the patient to regain his appetite, which had been lost because of dentures.

Another problem is that elderly persons frequently eat alone and live alone. A movement is afoot to establish eating clubs for them, where they may enjoy congenial company while eating. One of the basic considerations in geriatrics is nutrition. If food does not look good or taste good, or if the environment in which one eats is not good, one is likely to eat as a chore. This is almost incompatible with good nutrition.

MODERATOR KINSELL: Dr. Kark, have you any thoughts on that part of the problem?

DR. ROBERT KARK: I agree with Dr. Wilkinson. I also think that older people tend to lose their sense of smell, and in this way lose the enjoyment of eating. Moreover, they change their eating habits. Instead of having meals as they were accustomed to in younger life, they start eating frequently and become nibblers. Under such circumstances, they may eat completely unbalanced diets.

Another point concerns the digestive tract. Dr. Wilkinson has some data indicating that pancreatic secretion decreases in old age. Would you like to say something about that?

DR. WILKINSON: We use a nitrogen tolerance test. To a patient receiving a standard diet, we give a nitrogen load and measure the excess nitrogen excreted in the urine, rather than measuring the amount not absorbed in the stool. This is the reciprocal of the standard fecal nitrogen tolerance test.

We find that in many older people the absorption of nitrogen is decreased. Arbitrarily, I call this "pancreatic achylia" and am forced to call it "functional pancreatic achylia" because, in the few instances in which an autopsy was performed and we were able to examine the pancreas, it showed no degeneration. I am not sure of the mechanism, but I am convinced that there is decreased pancreatic secretion in some elderly persons.

DR. KARK: Old people may frequently have not only atony of the bowel, but also a disturbance of motility in the villi. As shown nearly fifty years ago, there is also a decrease in active propulsive movements. The person tends to become constipated, and this definitely reduces the appetite for food.

MODERATOR KINSELL: It is apparent, then, that one does need to have attractive food, companionship, the ability to masticate food, and the ability to digest food and absorb it, and that, unless the functions mentioned are all in reasonably good working order, the best diet in the world will avail nothing. If it is not consumed, it obviously will do no good, even if it is available. If it is not absorbed after being ingested, again, difficulties arise.

Dr. Wilkinson mentioned nitrogen. We are used to thinking of protein in terms of the total compound. You will recall that nitrogen is the material common to all amino acids, and it can be readily measured. If more nitrogen is in-

gested than is excreted, a person is in an anabolic state; that is, he is building tissue, since protein is one of the major components of cells. If a person excretes in the urine and stool virtually the same amount that he ingests, he is in nitrogen equilibrium and, therefore, should be able to remain in good condition. If he is losing more nitrogen than he is taking in, he is in a catabolic state. His balance is in the "red," and unpleasant things are bound to happen. More will be said about this later.

If a person is to grow old gracefully and to maintain tissue repair at a level compatible with age, he must have enough calories in addition to proper protein and other elements in the diet. Dr. Pollack might like to commence the discussion of this part of the subject. Tables are available which tell us about such matters, and Dr. Pollack knows a good deal about these tables and their background.

DR. HERBERT POLLACK: There is a dictum that a person can have a boxcar full of vitamin pills and another boxcar full of protein, but if he does not have enough calories he cannot survive long enough to utilize these accessory food factors. Calories are basic in the diet; they determine whether or not one is going to live. The total caloric requirement, which is the sum of the basic physiologic requirement plus the activity requirement, is the major calculation in establishing a diet for any group.

Decreased appetite in the aged is not an unmixed blessing, because as one grows older the caloric requirement decreases. The point is that, along with the decreased caloric intake of the aged, there should be a balance among the various components and accessory nutrients in order to maintain optimum nutrition.

Constancy of food intake with aging is bad. For instance, the maintenance requirement of a male 20 years of age is about 2800 calories a day. If such a man received 2800 calories a day for the ensuing thirty-five years and maintained the same physical activity, he would gain about 50 pounds, because as his age increased he would require approximately 10 per cent less food in each decade. In other words, for each succeeding year one lives beyond the period of maximum growth (about 25 years of age), 1 per cent less total calories are required. Thus, the total caloric intake must be decreased annually rather than being kept constant.

Older people may say that they eat no more than they used to, and yet they gain weight; they are absolutely right. The point is that they have not decreased their food intake in a degree commensurate with their decreased maintenance requirement. This is one of the fallacies of the National Research Council food and nutrition allowances. They allot too many calories to older people.

In a recent survey in New England, it was found that 50 per cent of the people over the age of 65 years were more than 10 per cent overweight, *i.e.*, they were obese. Only 30 per cent of them consumed the full National Research Council nutritional allowance. Obviously, if everyone consumed the full allowance, we would all be obese.

Thus, we must often be critical of the yardsticks made available to us with

regard to food requirements for the aging population. We must re-evaluate them in the light of our experience and the development of knowledge. The evidence is in favor of the concept that, although there is no decrease in the oxygen or energy requirement of active tissue per se, there is a decrease in total active protoplasm. The active protoplasmic mass decreases with age. This can be determined by the Archimedes principle of under-water weighing; a person is weighed in air and under water, specific gravity is determined, and the specific percentages of such body constituents as fat and bone are estimated. In aging populations, the ratio of active protoplasmic mass to oxygen requirement remains fairly constant. Shock and his group have established this, and I am prepared to accept the validity of their thinking.

MODERATOR KINSELL: The complex organism that we call a human being is made up of millions of cells. Each represents 1 unit of structure. There are many kinds of cells. Some are specialized, some unspecialized, and many intermediate.

To understand anything about aging or nutrition in relation to aging, it might be well to have some concept of the way in which cells are maintained. Are they equally self-perpetuating? Dr. Sperry, have you some thoughts in that connection?

DR. WARREN M. SPERRY: The biochemist and the experimental nutritionist have difficulties in applying their technics to the human subject under controlled conditions, as I am sure everyone can understand. Therefore, they have tended to turn toward animals.

Human beings, of course, are not rats. Still, one can learn something from studies on rats. I should like to refer briefly to 2 classic investigations, one in the field of nutrition and the other in the field of biochemistry. You will see that they overlap.

All of you have heard of the nutritional experiment conducted by McCay and his colleagues. In this study, the caloric intake of the rats was restricted. Incidentally, this has some bearing on what was said a moment ago. All of the essential factors such as protein, vitamins, minerals, and so on were given, but the calories were reduced in order to keep the rats well below normal weight. These rats lived far longer than their litter-mate controls, which were allowed to eat all they wanted of a regular diet. Not only did they live longer, but they looked like young rats. You may draw any conclusions you wish from this experiment. I am not going to elaborate further.

The other experiment related more to cells, and was carried out by Lowry, Hastings, McCay and Brown. They performed fairly complicated chemical determinations on rat tissues obtained throughout the life-span from youth to old age, and then applied certain calculations. Their findings were termed histochemical changes, although they did not mean what most of you would think of as histochemical. With aging, no significant change could be detected in the composition of the cells. Although it is frequently said that the tissues become wetter than usual, *i.e.*, contain more water, their calculations showed that that was not true. The only change was in the proportion of cellular mass or of intracellular fluid to extracellular fluid. There was little or no change of this sort in

the liver, which apparently continues to regenerate and grow even in old age—at least in rats. The same was true of the brain; but in muscle and kidney a considerable change in the proportion was found; that is, in the old rats, the proportion of cells in the total mass of tissue became smaller. However, each separate cell had about the same composition as in young rats. Finally, Lowry and his colleagues studied some of the rats that had been retarded by the Cornell group and found that in these old animals (some of them equivalent in age to a 90-year-old human subject) the composition of muscle and kidney was much the same as in young rats. Retardation had resulted in the maintenance of muscle and kidney tissue in a relatively youthful state. The implications of these findings are evident.

MODERATOR KINSELL: Would any other member of the panel want to complete the information about the rules that concern the cells in the body? Dr. Kark, you would be just the person to do that.

DR. KARK: No one has all the rules. It is obvious to anyone looking at an elderly person that one of the major signs is the change in the skin—wrinkling and thinning. This reflects changes throughout the body.

Most of us have been made aware in the past few years of an organ system composed of ground substance and connective tissue. This is really one system. The ground substance consists of mucopolysaccharides that lie between the cells. These mucopolysaccharides exist in both a water-rich and a water-poor phase. They are secreted by cells into the spaces between cells. From the mucopolysaccharides, arise the ground substances, elastin and collagen.

Those who have been interested in this problem recognize that connective-tissue reacts to various types of endocrinologic stimuli. However, except for some studies on starvation, we know little about the effect of nutrition upon the ground substance and connective tissue. This field is open for research. Dr. Wilkinson may have something to say about this.

MODERATOR KINSELL: Dr. Wilkinson, have you any comments?

DR. WILKINSON: I have nothing to add.

MODERATOR KINSELL: Would you like to say something, Dr. Graef?

DR. IRVING GRAEF: It has been said that we all begin to die at birth. There are some indices of the dying process in the desquamation of cells lining the surfaces of internal cavities or hollow organs and the cells of the epidermis. In the supporting tissues, the changes associated with the passage of time have been observed by all of us and measured in detail by some.

Anthropologists seeking evidence of the aging process in old skeletons and in living persons have agreed that certain changes in supporting tissues and perhaps in certain proteins are associated with the passage of time. The well known phenomenon of the onset of presbyopia in the fifth decade is due to a change in the crystalline protein of the lens.

The calcification of cartilage at the ends of the ribs, especially of the second rib, has been used as an index of aging with a high degree of accuracy in large samples that have been studied and compared.

Dr. Kark has referred to the loss of elasticity associated with the great change

in the skin of the aging person. One may also refer to the loss of elasticity in the aorta (the ground substance of the aorta and the elastic fibers in particular), the loss of elasticity in the fibers that support the alveolar structure of the lung, and to a change in bone structure that is associated with a thinning of osteocollagen (the supporting matrix for the minerals that give osteocollagen its rigidity).

The well known phenomenon of osteoarthritis may be recalled in this connection. To what extent this represents a pathologic event associated with age, and to what extent it represents a metabolic derangement, is still not clear.

As far as I know, nutritional factors have not been correlated with either the protraction or the deferment of this phenomenon. It would be interesting to learn from McCay's rats whether or not some of the findings so common in human beings with the passage of time are altered by undernutrition in the growing animal.

Apparently no hallmarks are associated with changes in the nutritional state and in the supporting tissues. The only common denominator, as far as I know, is the passage of time.

MODERATOR KINSELL: The beginning of old age is being perpetually pushed back, at least as far as one's thinking is concerned. This may have been noted by some of the people in the room.

With regard to aging of specific tissues, let us consider, for instance, the changes in the crystalline lens. Are they immutable, are they built into the time clock, and do they represent something which we can never do anything about; or are they preventable when we have the knowledge?

DR. GRAEF: I should like to say "yes" to the second alternative, but I am trying to be "scientific." Therefore, I can only say that I do not know.

MODERATOR KINSELL: Just an educated guess so that we can check on your guess five or ten years hence.

DR. GRAEF: I have only one quick reply that has some bearing on the subject. It is interesting to make reference to the changes in the lens observed in hyperglycemic states. Acute experimental diabetes is associated regularly with a reversible change in the crystalline structure of the lens. This may give us some clues as to how the aging process takes place, but I know of no physiologic mechanism that alters or defers the change observed in human beings.

MODERATOR KINSELL: Dr. Kark.

DR. KARK: Although I have no laboratory data, I have some observations on the relation between nutrition and aging. I have studied a number of population groups. In alcoholic populations there is often clinical evidence of early aging. In working with people who unfortunately have a craving for alcohol, you may observe a man who appears to be somewhere between 50 and 65 years old; you talk with him and find that he is only 35 or 40. This has always been surprising to me.

This summer, I happened to be in North Africa studying nutrition among the Arabs of Libya. They live on a diet composed mainly of carbohydrates. The fat intake is about 8 per cent. The protein intake is low by our standards—about 10 per cent of the total calories. This diet is deficient in calories, and the fat

intake and protein intake are low by our standards. The aging process there was fantastic. We examined a number of women aged 20 to 25 years. They appeared to be very old; in fact, they looked like ancient crones. Whether this was due to their having had babies every year, as well as being undernourished, I do not know. They certainly were aged by any standards of clinical observation.

The same was true of people that I examined in India during the war. Again, there was a low-fat, low-protein and high-carbohydrate intake.

DR. POLLACK: May I add something to that, please?

MODERATOR KINSELL: Please do, Dr. Pollack.

DR. POLLACK: I should not like to see this subject dropped without mentioning that there is another side.

McCay's experiments are classic, but we must not neglect the fact that McCullen and Sherman at about the same time showed that rats could live a long, long time when fed a diet, not high in calories specifically, but high in certain specific vitamins and in certain types of protein. Furthermore, hyperalimented rats that lived a long time had more litters. They were more potent sexually. One sometimes wonders whether or not other ancillary things are correlated with eating well.

MODERATOR KINSELL: Since you mentioned the word protein, and since it has been mentioned a good many times this morning, it might be well to ask Dr. Allison to give us his thoughts about protein requirements at different age periods. Is it a good thing to take as much protein as one can possibly eat? Is it well to take the minimum amount that one can get along with? From the preceding discussion there would appear to be less than total agreement regarding this point. I know of no one better prepared to clarify this for us, at least in terms of available knowledge, than Dr. Allison.

DR. JAMES B. ALLISON: Thank you for the opportunity to talk about protein requirements. We can estimate the absolute nitrogen requirement for growth and maintenance at different ages but, unfortunately, the estimates for elderly people are based upon scanty experimental data.

The total amount of protein required by a baby fed mother's milk from birth to the age of 1 month would be about 2 Gm. per day per Kg. of body weight. That amount of mother's milk protein would supply the needs for both growth and maintenance.

The requirement for growth decreases as the child approaches adulthood. The absolute minimum requirement for maintenance is close to 2 mg. of nitrogen or 12.5 mg. of protein per basal calorie. A certain additional quantity of protein must be added to the diet for growth. For example, the Committee on Protein Requirements of the Food and Agricultural Organization estimated the minimum protein requirement at age 2 years to be approximately 1 Gm. of protein per day per kilogram, dropping to 0.7 Gm. at age 9 years. There is a peak during adolescence that would amount to about 0.8 Gm. per day per Kg. of body weight for either a boy or a girl. At age 25 years, when growth has stopped, the absolute requirement of protein for maintenance would be approximately 0.4 Gm. per day per Kg. of body weight.

It should be emphasized that these are estimates based upon minimum re-

quirements of a protein of high nutritive quality. The so-called protein reserves also would be minimum. Approximately 1 Gm. of protein in an average American diet would be required for maintenance instead of the low figure of 0.4 Gm. just mentioned. We can adapt to high-protein and low-protein intakes by this increase and decrease in what are often called protein reserves, or a metabolic pool of proteins. These reserves are proteins such as plasma albumin and the cytoplasmic proteins of the cells of the liver, intestinal tract, and other soft tissues of the body.

As a person grows older, the requirement for calories decreases. Possibly the requirement for protein to maintain nitrogen equilibrium also decreases. Therefore, I would estimate that in old age about 0.3 Gm. of an ideal dietary protein per day per Kg. of body weight would be adequate. This intake would be an absolute requirement. I would guess that the biologic value of the average diet eaten by elderly people would be about 60, so that under ideal conditions the elderly person needs at least 0.5 Gm. of protein per day per Kg. for maintenance. Taking into consideration that absorption may be poor and other abnormalities present, the minimum daily requirement would again be nearer 1 Gm. per day per Kg.

One of the primary problems encountered in elderly persons is the repletion of tissues depleted by illness and/or restricted food intake. Repletion of depleted tissues is a function of nitrogen intake, quality of protein, and caloric intake.

These functions are illustrated best by data obtained on animals, because we do not have an opportunity to secure this type of information from experiments on people. Our problem was to replete the depleted tissues of adult animals, some of which were quite old. Most of the proteins to be repleted belonged to enzyme systems needed by the body for optimum health. In a depleted dog, 0.6 Gm. of protein nitrogen and 70 calories per day per Kg. of body weight did not completely replete the animal's tissues. When the intake of protein nitrogen was increased to 1 Gm. per day per Kg. and the caloric intake kept at 70, the rate of repletion remained the same, but the amount of repletion became much greater. However, when the caloric intake was increased to 140 calories per day per Kg. (approximately the amount required by the growing puppy), the rate of repletion increased tremendously. This very close inter-relation between caloric and nitrogen intakes always must be taken into consideration in developing a diet, particularly for purposes of repletion.

The animal fed 1 Gm. of protein nitrogen per day per Kg. for repletion actually required only about 0.3 Gm. of protein nitrogen per day per Kg. to maintain the repleted tissues.

Other data demonstrate that with protein of lower biologic value, the rate of repletion is less, and much more protein must be included in the diet. Thus, the amount of protein in the diet will depend upon the caloric intake, the nitrogen intake, and the biologic value of the protein. It is, in a sense, a three-dimensional problem.

MODERATOR KINSELL: Will you please say a few words about what you mean by the biologic value of a protein in terms of amino-acid composition?

DR. ALLISON: That is really an important question. Let's put it this way. The body needs a certain pattern of amino acids to synthesize tissue proteins, and the dietary proteins supply that pattern of amino acids. The body can synthesize some of the amino acids, but there are some which must be in the diet every day, just as certain vitamins must be in the diet every day. We call these essential amino acids.

If the dietary protein is somewhat low in one of the essential amino acids needed by the body to synthesize tissue protein, more of that deficient protein must be fed to provide the quantity of the deficient amino acid needed for tissue synthesis. Wheat gluten, for example, is deficient in the essential amino acid, lysine. Therefore, about twice as much wheat gluten must be fed to meet the requirements for tissue protein synthesis as would be needed if milk protein were being fed. The biologic value, then, is an attempt to express the efficiency of the dietary protein in building tissue protein, the efficiency being correlated with the pattern of essential amino acids that the dietary proteins supply to the body.

MODERATOR KINSELL: Thank you, Dr. Allison.

DR. WILKINSON: Isn't it true, Dr. Allison, that if any two or any three sources of natural protein are mixed, one has a good and complete source of protein?

DR. ALLISON: In fact, you can mix many vegetable proteins that are deficient in some essential amino acids, like lysine and the sulphur amino acids, and obtain an excellent dietary protein. Animal protein supplements vegetable protein nicely. Our problem in America is to determine the optimum protein intake for different age groups for the development of optimum protein reserves.

MODERATOR KINSELL: It is perhaps not incorrect to say that clinical nutrition is taught less well in medical schools than almost any subject one can mention, and practiced less well than almost any part of clinical medicine. This is sad, because much information is available that we are not using adequately. We give vitamin supplements to people without much thought as to why and how. We do not know all the answers. There is much to be done in this field, and much will be done in terms of principle, teaching and practice over the years immediately ahead.

Perhaps those who have been most cognizant, or most conscious, of the need for dietary management and for precise dietary information in clinical medicine are men in clinical practice who see many patients with diabetes. This is a metabolic disease, a dietary disease, that involves all these factors. Perhaps Dr. Graef would be the one to expound on some of the comments that have already been made regarding the need for other sources of calories in the diet in order to spare protein, in order to utilize protein, in order to repair tissue, in order to maintain a good energetic individual and, one would hope, in order to deter the aging process so that it does not move any faster than necessary.

Dr. Graef, would you like to speak of those things?

DR. GRAEF: I shall try. The matter of estimating caloric requirements requires a sense of art as well as precision. It depends on where you start. If you are dealing with a sick person who has been undernourished for a variable and probably unknown period of time, it is a simple matter to make the assumption

that the provision of adequate protein in the diet, plus supplements of carbohydrates and fat, may not only meet his current caloric requirement but aid him in restoring his reserves and in healing injured tissue. In clinical nutrition, when dealing with relatively healthy subjects, one has to take into account what the person is, or has been, doing.

In diabetes, we are constantly charged with the need to estimate the role of muscle metabolism, that is, muscular work, in the utilization of readily available or extra glucose. We try to adjust the intake of readily available exogenous glucose and sources of glucose, in such a manner as to avoid persistent hyperglycemia. If this requires the addition of insulin, we use insulin, desiring to keep our patient normoglycemic in the broadest sense of that adjective.

Physical activity in the aged person reflects his capacity, or his idea of capacity for muscular performance. Here, social attitudes, cultural practices and other opportunities play roles that I need not emphasize. We see the unemployed sedentary person who is a replica of Whistler's mother, sitting in front of a television set, perhaps consuming a third of the potential calories that he or she might utilize under circumstances of arduous work. I need not remind you that in our gadget-cluttered civilization, it is a much shorter step from the refrigerator to the electric stove than it used to be from the kitchen to a smoke house, or the place where the hams were, or to where hens were laying eggs. Muscular performance in an older person declines either voluntarily or involuntarily, or unconsciously. All of us, in taking into account caloric requirements, are well aware of the role of active exercise in determining them.

The same increments of caloric requirements can be related to muscular performance in older persons. From my point of view, tone, in the broadest sense of that word, requires work, and this work load must be met.

In an actively exercising or actively working person who is apparently well, the protein requirements approach those of a younger person, provided absorption is normal. When protein may not be absorbed readily because of a deficiency of enzymes in the digestive tract, it may well be (I know of no studies to support this) that lipolysis is likewise deficient to some extent. Nevertheless, carbohydrates and fat are more readily available for energy than is protein. Their protein-sparing action needs no emphasis.

The need for appraisal of the deficiency state in prescribing diets for older persons cannot be stressed too strongly. Wartime studies of convalescent injured troops showed clearly that, though resting, the caloric requirements for reduction of healing time were much greater than we had previously supposed. Healing times were shortened as much as 50 per cent by increasing total calories, with due attention to the sparing action of fat and carbohydrate and to the provision of basic protein requirements. When protein is supplemented as such, the additional protein provides extra calories and storage will take place. However, we have to take into account what constitutes a palatable, attractive and easily digested meal. Here, the art of dietetics becomes essential.

Personal tastes must be taken into account. These are related to cultural habits and the practices of many generations with respect to a given person.

We know how easy it is to drift into the practice of inadequate nutrition. I suppose everybody in this room has seen the person who changed from the busy American's breakfast of orange juice, coffee and toast to a cup of coffee and a cigarette, and who takes tea and toast or coffee and toast or just coffee, and another cigarette as a supplement!

The need to provide additional calories in balanced form cannot be overemphasized. Not only is there the matter of completeness of protein, but also the factor that additional calories derived from protein, fat and carbohydrate will spare body protein to a considerable extent. Estimates will vary greatly according to the total caloric requirements of the person based on his or her activities.

MODERATOR KINSELL: Thank you very much, Dr. Graef.

In the second part of the discussion, we shall have an opportunity to comment on the optimal relationships of fat, protein and carbohydrate in the diet.

The use of protein to the point where much of it is utilized for fuel could perhaps be compared to the general idea that one can heat a house by putting regular fuel on a fire, but one can also chop up the piano and burn it. Both methods will provide calories, but the piano-destruction procedure has certain undesirable features.

Before we leave the discussion of protein per se, would any one on the panel like to comment briefly as to whether or not he thinks that protein above a certain level may actually be undesirable in the diet? I do not mean in terms of providing too many calories and thus leading to obesity. Given a diet compatible with an optimal weight, is it better to use 60 Gm., 100 Gm., or 150 Gm. of protein?

DR. WILKINSON: Before that question is answered, may I comment on the remarks by Dr. Graef?

MODERATOR KINSELL: Certainly.

DR. WILKINSON: It is true that certain amounts and types of work require certain amounts of energy, but Hellerstein in this country and several investigators in Scandinavian countries have reported actual work requirements. Hellerstein's observations were made primarily during the rehabilitation of patients after coronary thrombosis. He has found that many jobs in the steel mill require the expenditure of less energy by a man than if he were to stay at home and help around the house. This has to do not only with the efficiency that a person brings to the job but also with the actual expenditure of energy. We frequently think that the housewife has an easy job. Actually she performs a lot of work. Whereas the laundry used to be sent out, she now carries it downstairs to the washing machine. This requires energy.

MODERATOR KINSELL: Is there any further comment?

DR. POLLACK: I should like to point out one minor thing. When we are dealing with a human being, we are dealing with a composite of a number of organs. We have to establish priority in designing therapeutic diets.

Obviously, when dealing with any element of renal failure or renal dysfunction, an attempt to reach an optimal protein intake will endanger the life of

the patient by virtue of the renal dysfunction. In some of our studies in which we forced proteins in feedings as high as 250 to 300 Gm. per day—ridiculous figures except under certain circumstances—it was a comparatively simple matter to increase the blood urea nitrogen level well over 100 mg. per 100 cc. Let us not focus so sharply upon physiologic requirements that we forget we are dealing with a composite of organs, each of which has to take up the slack when we alter or deviate from an established pattern.

MODERATOR KINSELL: We shall proceed now to micronutrients. After this discussion, questions will be accepted from the audience. You might all start thinking about possible aspects on which you would like more information. Dr. Pollack, will you say something about micronutrients?

DR. POLLACK: First of all, we should analyze the functions of the various micronutrients, some of which are called vitamins. By such an analysis, we can assess their proper values in the diet and the importance of increasing or decreasing their intake.

The B vitamins, particularly, are associated with the enzyme and co-enzyme systems basically involved in the utilization of many foodstuffs. These enzyme and co-enzyme systems are combinations of proteins and vitamins. Therefore, we cannot differentiate or separate the protein story entirely from the vitamin story, as Dr. Allison has inferred.

Once the growth period is over, that is, beyond the age of 24 or 25 years (maximum limit), we reach a period of stabilized requirements for both protein and vitamins. Vitamin requirements do not change particularly with aging. There is little, if any, evidence that the elderly person requires more vitamins for his metabolic functions than does the younger person.

I want to differentiate clearly between the theoretical requirement and the actual clinical observation. Sometimes in older persons with absorption problems, the dietary components must be increased in an attempt to compensate for the decrease in absorption; nevertheless, the actual physiologic requirement of the body per se is somewhat less because the metabolic requirement of the aging person is less than that of the younger person. Since, as we established, the requirement of B vitamin is related directly to metabolic needs, it follows that the requirement of B vitamin will be decreased to some extent as the total metabolic needs decrease.

Again, let me emphasize that this is a physiologic requirement and not a dietary one, because the latter must be adjusted to the ability of the gastrointestinal tract to transfer the dietary intake to the body economy. This is a subject that Dr. Kark and Dr. Wilkinson referred to in the discussion.

One of the problems of mineral metabolism in aging people involves osteoporosis. Whether or not this is a dietary problem remains to be seen. Certainly, it is related more to endocrine factors than to dietary factors. The forced feeding of calcium tablets by mouth in an attempt to overcome osteoporosis is not the proper approach to the problem, and consequently no therapeutic success is achieved. In these cases, the protein and hormonal requirements are even more important than the mineral requirement.

There is a large field for the development of endocrine supplements for elderly patients. We know, for instance, that hormones and vitamins can supplement or replace each other to a certain extent. Some years ago, this relationship was established between parathyroid hormone and vitamin D. It was found that symptoms of vitamin D deficiency could be relieved by the administration of parathyroid hormone and, conversely, that symptoms of parathyroid hormone deficiency could be relieved by the administration of vitamin D. Each compound exerts its effect on the blood calcium level through somewhat different mechanisms, but they supplement or complement each other in the overall clinical effect, which, after all, is the ultimate goal.

The alterations in dietary requirements within various age groups are important from the point of view of the basic physiologic requirement, as the two are not necessarily similar at all times.

MODERATOR KINSELL: Since there may be impairment of absorption of various essential nutrients by the digestive tract in the older age group, should we routinely supplement a diet with a multivitamin preparation? Should we prescribe tailor-made vitamin mixtures, or should we not prescribe any vitamin preparations?

DR. KARK: I agree with Dr. Pollack. It is well known that vitamin deficiencies occur in the young, the aged, the uninformed, the food faddists, and the poor. As far as the older population is concerned, it is well known, for example, that pellagra occurs in endemic areas in both the old and the young, but not in the intermediate age groups.

In the absence of signs of malnutrition, dietary therapy for older people should attempt to provide a well balanced diet instead of an unbalanced diet supplemented with vitamins. Every older person who comes to a physician should be examined, not only for cancer and other diseases of old age, but thoroughly and carefully for the early signs and symptoms of malnutrition.

If a patient cannot be induced to eat a decent diet, or if the physician finds even minimal signs of malnutrition, the patient should be treated with vitamins. I do not favor supplying vitamins to all the members of one group at any age.

MODERATOR KINSELL: Would you like to give us the major areas that you would check routinely for evidence of nutritional deficiency, Dr. Kark?

DR. KARK: Some of the changes in the mental processes of older people may be due to malnutrition. This is a hard field to work in without therapeutic trial. If there are changes in a patient's mental attitude and he suddenly complains that he cannot sleep, one has to think about a thiamine or niacin deficiency. The only way to test this diagnosis is by trying vitamins and then discontinuing them to see if a relapse occurs.

One ought to look for such signs as cracks in the skin around the backs of the ears and at the sides of the eyes, nasolabial seborrhea, cheilosis, cheilitis, sore tongue, atrophy of the tongue, changes in the nails, crackled skin on the legs, and mottling of the hands. These minor signs may possibly indicate malnutrition. If they are associated with a history of poor dietary intake, or if they respond to vitamin therapy, the evidence is in favor of vitamin deficiency.

MODERATOR KINSELL: Thank you very much, Dr. Kark. Has any other member of the panel a comment?

DR. POLLACK: I should like to re-emphasize the interrelationship between these various nutrient groups and factors. For instance, in certain types of acute loss of protein from the body, one can give riboflavin *ad infinitum* and not cure the riboflavin deficiency, because the protein is in a catabolic state and not available for combination with the riboflavin in order to synthesize the functional components of the enzymes.

Let us not be hasty in blaming a specific vitamin for a group of deficiency syndromes. Let us bear in mind that possibly the condition is due to an overall metabolic insult to the body that has resulted in an indicator lesion which we are pleased to call a deficiency syndrome. This is a manifestation of a total metabolic insult rather than of a deficiency of any one vitamin in the diet.

DR. KARK: That is very important. I agree that when there are signs of a specific vitamin deficiency, there will also be a general deficiency syndrome in nearly every case.

MODERATOR KINSELL: There are many things upon which we have not touched, but we shall now take up questions from the floor.

DR. GRAEF: Dr. Kinsell, may I ask Dr. Kark or Dr. Pollack to comment on the recent evidence for the existence of iron deficiency states without overt evidence of anemia or clinical evidence suggesting iron deficiency? Work carried out in Chicago and reported last year has a bearing on this particular micronutrient.

DR. POLLACK: I have been too busy with lipids lately to know what you are talking about.

DR. GRAEF: It is the existence of iron deficiency in the tissue without evidence of anemia. This work at the University of Chicago was reported in May by Buetler at the Society for Clinical Investigation.

DR. KARK: This condition is presumably due to a deficiency of erythropoietin, which is produced by the body when there is any kind of anemia. This concept is under attack by those who disagree with Dr. Leon Jacobson's ideas.

Pernicious anemia is a disease that often appears in old people. However, Dr. Witts at Oxford has shown that, in families in which pernicious anemia is found, the younger members may have achylia gastrica (absence of the intrinsic factor and of hydrochloric acid) without any clinical evidence of pernicious anemia. It is only when they grow older that overt signs of the disease develop.

MODERATOR KINSELL: Have we questions from the floor?

SPEAKER FROM THE FLOOR: I see many people who take mineral oil daily as a laxative. It has been said that mineral oil often hinders the absorption of vitamins. Is this true, and if it is, does it do any good to give those people vitamins?

Second, in older people with osteoporosis the continued administration of hormones seems to do no good. Is there any particular reason why it does not do any good?

MODERATOR KINSELL: Who would like to take the question about mineral oil?

DR. POLLACK: I will take it because it happens to be a pet topic of mine.

Mineral oil does interfere with the absorption of the fat-soluble vitamins, particularly vitamins A, K and E. One of the major problems in elderly persons who take excessive quantities of mineral oil at the wrong time of day is vitamin K deficiency. Not infrequently, in such elderly people one sees purpuric lesions, that is, ecchymoses and black and blue spots all over the body. By discontinuing mineral oil, one can usually get rid of the purpuric manifestations which are obviously due to vitamin K deficiency induced by administration of mineral oil.

Mineral oil, taken with a meal or shortly thereafter, will exert a preferential solubilizing action. As it comes out in the stool, it is usually an intense yellow color because it has picked up most of the carotene or vitamin A. Mineral oil taken at bedtime, several hours after a meal, fortunately does not have the same deleterious effect as when taken as a salad dressing in a reducing diet, where it simply picks up the carotene in the vitamin A of the salad and prevents it from entering the metabolic economy of the body. We usually advise against the use of mineral oil. When it is used, we recommend that it be taken at bedtime, many hours after a meal, and the quantity limited.

DR. WILKINSON: May I make a comment on that?

MODERATOR KINSELL: Yes, Dr. Wilkinson.

DR. WILKINSON: I am one who uses mineral-oil salad dressings in reducing diets. I do not believe that the amount of mineral oil commonly used in a salad dressing in a reducing diet has any great effect on the amount of vitamins absorbed. On the other hand, one can fortify the mineral oil. Certain brands of fortified mineral oil on the market are saturated. Saturated mineral oil can absorb no more.

MODERATOR KINSELL: Your moderator will vote with Dr. Pollack. I would toss Dr. Wilkinson's statement about the amount of mineral oil back at him by saying that the amount of fat in a little bit of mayonnaise is not much and the caloric problem there is not a large one; moreover, it is a nice way to get a little essential fatty acid. Dr. Kark says we can discuss that in the second section.

Dr. Wilkinson, do I recall that you had some thoughts about hormones and osteoporosis? Do you routinely "hormonalize" all, or none, of your patients past a certain age? If they have osteoporosis, do you cure them all? What are your thoughts?

DR. WILKINSON: I asked the question; I did not answer it. I thought the panel should be prepared to answer it, so I shall toss it back to them.

MODERATOR KINSELL: May I have the comments of other panel members?

DR. GRAEF: Clinical experience with this subject ought to be tempered with the knowledge that the measurement of osteoporosis by x-ray technics is difficult.

Albright's early observations, based on storage and balance data and on estimates from radiograms, indicated that the osteoporotic process could be arrested and that increased density followed the use of anabolic steroid hormones.

I know of no clean-cut experiment that shows that the analog of human osteoporosis can be reversed in experimental animals. That calcification can be increased in many subjects with osteoporosis appears to be clear.

The questions of dosage, duration of the osteoporosis, and whether there is a

point where it is no longer reversible, remain open for inquiry. I am not convinced that the evidence in clinical studies indicates that recalcification occurs. What does not occur is the laying down of osteocollagen, except in the areas of injury.

MODERATOR KINSELL: One of the puzzling things has been the fact that great numbers of people with severe osteoporosis (including compression fractures of the spine), when given estrogen or estrogen with a little testosterone, experience remarkable clinical improvement with regard to pain and functional capacity. However, roentgenograms taken of the spine and other bones any time from six months to two years later usually look just about the same as they did at the time therapy was started, despite the major clinical improvement and the retention of appreciable quantities of nitrogen, phosphorus and calcium, as shown by metabolic balance studies.

The consensus of most physicians is that anyone with osteoporosis should receive anabolic steroids, calcium pills and such. It is essential that the diet contain adequate amounts of proteins, as osteoporosis in a real sense is a protein deficiency or protein anabolism deficiency disease, and only secondarily a calcium and phosphorus deficiency disease.

Whether all postmenopausal females, since they are so much more subject to osteoporosis than are males, should receive prophylactic therapy with estrogen is a moot question. I would favor it. This, too, we can bring up in the second part of the discussion about the relation of steroid hormones to certain aspects of lipids.

Are there any other questions from members of the panel?

DR. POLLACK: We ought to remember that there are several components of osteoporosis. Before we knew much about hormones, calcium, and so forth, we saw the osteoporosis of sailors who were below deck in the days when they had to shovel coal. The shovelers would not see the deck for days or months on end. This was the type of osteoporosis that came into Bellevue in the early days.

Then, there is the type of osteoporosis that we saw during the war in the famine areas of Holland and in Paris—so-called Milkman's disease, which was directly attributable to a nutritional deficiency and which was reversible with refeeding.

Then we have the osteoporosis of the aging, or the menopausal female, which is still somewhat of a mystery, but which is obviously due to a mixture of a dietary and hormonal factors.

SPEAKER FROM THE FLOOR: I want to ask Dr. Kark about the possibility of testosterone producing malignancy of the prostate.

DR. KARK: I do not use testosterone in my patients. I did not say that, did I?

SPEAKER FROM THE FLOOR: No. I want to know your opinion.

DR. KARK: It is hard to form an opinion on this subject. If one cuts serial sections of the prostates of older men, he will nearly always find an area that looks malignant. The problem is whether the area that looks malignant has metastasized or not. I doubt that large amounts of testosterone produce cancer. I think that this has been overstressed.

SPEAKER FROM THE FLOOR: Thank you, Dr. Kark.

MODERATOR KINSELL: Are there other questions?

SPEAKER FROM THE FLOOR: Are there any blood levels of micronutrients—vitamins, minerals, and so forth—that might be considered normal, so that one can judge whether or not a patient is taking adequate amounts of vitamins and assimilating them?

DR. POLLACK: Yes, there are such standards for both vitamin A and carotene. Normal blood levels are well established for vitamin C and other nutrients, as are urinary excretion, hourly output, and the ratio of the amount of vitamin to the amount of creatine in the urine.

The validity of these established values is still open to question. Certain yardsticks may have been set up entirely on the basis of statistical experience. It is almost impossible to correlate the data for any one person with the statistically established blood levels. In a mass population study in which from 700 to 2000 people are involved, one can establish a definite relationship between the incidence of deficiency syndromes and these blood and urine levels. However, for any one person, this relationship will not hold true at all times.

MODERATOR KINSELL: We shall have one last question from Dr. Graef.

DR. GRAEF: Dr. Wilkinson, what preliminary preparation do you make for nitrogen tolerance studies in your patients? What is your source of nitrogen and the amount used in such a test? Does the test relate chiefly to disturbances in digestion and absorption, or to the nitrogen after it enters the body?

DR. WILKINSON: I shall answer the last question first. We assume that a nitrogen load will not alter the nitrogen balance immediately. In other words, a greatly increased nitrogen intake at one meal cannot be utilized completely, even if the person is in a state of negative nitrogen balance.

We use a standard diabetic diet, because at Bellevue it is the easiest diet to order and be sure of what we get. We add to it 300 Gm. (preferably 400 Gm.) of ground beef at breakfast. Reasonably accurate results can be obtained with as little as 100 Gm., but we do not feel satisfied unless we can give at least 300 Gm.

PART II

MODERATOR LAURANCE W. KINSELL: We have come a long way, but I would stress that we have a much longer way to go before the lipid picture comes into focus. There are, however, at least two good things about the study of lipid metabolism. First, there is a path to follow. It is not an easy path, methodologically or otherwise, but it is a reasonable path and one that will lead us eventually to a better understanding of the role of lipids in general and in human metabolism particularly.

Secondly, there is a decline of the tendency toward hysteria in this field, particularly in the high places where it is most unbecoming. Many of us are progressively realizing that much more is accomplished by working hard and avoiding broad generalizations based on one and a half pieces of data.

That people do die from coronary heart disease undoubtedly has something to do with a tendency toward hysteria. That we do have a tremendous increase in the number of older people around us has something to do with it. I think it might

be well at this moment to stress that when we say that the life span has been increased, we are not talking about increasing the ability of a man already 50 years old to live longer, but about increasing the number of people who reach age 50.

Let us go from generalities to specificities and ask Dr. Allison to start this session with some comments about the balance among nutrients, with particular reference to fat, carbohydrates and other dietary entities.

DR. JAMES B. ALLISON: I want to reemphasize that we must have a balance among all dietary constituents—proteins, carbohydrates, lipids, minerals and vitamins. Each constituent in the diet has a specific job. Sometimes, for example, we lump fats and carbohydrates together as sources of calories, but each has its specific role to play.

I am reminded of the work of Dr. Monroe—work that illustrates one of the specific roles of carbohydrates that is not well known. Monroe interpreted his data as follows: When carbohydrate is absorbed into the blood stream, the hormone insulin is stimulated. One of the responses to this metabolic shift is the piling up of amino acids in the muscle cells. A temporary nitrogen retention results, which is an interesting specific effect of carbohydrate, not found with fat. Both fat and carbohydrate are important dietary constituents as sources of calories, but there should be a definite balance between them. Fat has a specific role of supplying unsaturated fatty acids.

I do not need to expand this discussion further except to emphasize again the important problem of balance, not only for amino acids but for all of the various constituents in our diet. This balance can shift with age or the physiologic state of the individual.

MODERATOR KINSELL: Thank you, Dr. Allison. Some of the information in this area is available, and much more will become available. It is an area of great importance. The old statement that fats burn in the fire of the carbohydrates, which for a long time was discarded, has crept back to a certain extent.

It might be in order for one of the panelists to review briefly some of the major lipids that are biologically important, particularly those present in the human body or related organisms. Dr. Sperry.

DR. WARREN M. SPERRY: Lipids may be defined either from a chemical point of view or a physical one. Chemically, they are defined as derivatives of fatty acids. They may occur in the body in combination with fatty acids, or in the free state. Cholesterol is such a compound.

The physical definition most widely employed is based on solubilities. From this standpoint, lipids are defined as compounds which occur in living things and are soluble in the conventional fat solvents—ether, chloroform, and so on. This definition includes many compounds or types of compounds that have nothing to do with fatty acids, such as the fat-soluble vitamins, steroid hormones, and carotene. Those of us who work with lipids do not think of these compounds as being lipids at all.

Lipids, according to the fatty-acid definition, include an exceedingly complex group of substances. In the tissues, in brain in particular, you will find such bizarre and exotic things as the gangliosides. glycosphingosides, phosphosphin-

gosides, and strandin. Many of these substances have not yet been isolated, and some of them may not be exclusively in the brain. There is evidence that they occur, but in much smaller amounts, in other tissues. In the blood, where most interest has been focused, there are only 4 lipids which are the subject of much discussion. Both cholesterol and cholesterol esters are included, as recent evidence points more and more to the importance of cholesterol esters in relation to essential fatty acids. The other 2 groups are the triglycerides (ordinary fat) and the phosphatides. Phosphatides comprise a large complex class of substances. In the serum most of the phosphatides are in the form of lecithin, with some sphingomyelin and very little cephalin.

These substances do not occur in the blood stream as relatively simple compounds. They are present almost exclusively in combination with protein as lipoproteins. There is one possible exception, *i.e.*, chylomicrons, which are almost all lipid but probably also contain a little protein. The data indicate that they also are lipoproteins in which there is a very small amount of protein carrying a large amount of lipid.

Some of you may have heard the word proteolipid, which is the type of substance now being studied a good deal in brain tissue. The terms lipoprotein and proteolipid have no relation to the proportions of lipid and protein, but refer only to the physical properties. A lipoprotein behaves like a protein, being soluble in aqueous media and insoluble in fat solvents. A proteolipid behaves like a lipid, being soluble in fat solvents and insoluble in aqueous media. There can be a lipoprotein that is almost all lipid, and a proteolipid that contains a high proportion of protein.

MODERATOR KINSELL: Thank you, Dr. Sperry. This gives us the background to build upon.

Would you want to say anthing about lipids and cell membranes? Is there enough information to transpose into clinical thinking, or would this be premature?

DR. SPERRY: Actually, there is little good evidence. On the basis of physical properties, it has been assumed that lipids tend to concentrate in cell membranes. There is some definitive work, including quite a bit on the red cell. It has been shown that lipids are largely concentrated in the stroma. Evidence is now accumulating that these substances are present in the various structures of the cell. The biochemist is knocking cells to pieces and studying the mitochondria, the microsomes, the nuclei, and so on. Lipids are found in all of these. There is evidence that the enzyme systems present in the mitochondria contain large proportions of lipids; they are lipoproteins. Dr. David Green believes that they are concerned with the actual process of metabolism carried out by these enzymes.

MODERATOR KINSELL: That is exactly what I had hoped that you would bring out. We have all been led to think of amino acids and large aggregate proteins as being the components of cell structure. As knowledge accumulates, we shall be thinking also of lipids as components of cell structure. This will confuse us, but perhaps only for a while.

There is no area in which people are more confused than in the matter of

the relation of diet to coronary heart disease, as there has been so much superficial talk and so little understanding, of basic things relating to lipids. Perhaps, if we can clarify some points and get a real understructure upon which to build, some of these things will be less confusing; even atherosclerosis may make some sense eventually.

In an approach to clinical applications as well as to the whole field of lipids, it might be pertinent to think of the factors involved in running machines. In the course of the day, one burns a good many calories. The possible sources of those calories we discussed a while ago. There is increasing evidence that fatty acids constitute the major fuel that runs the machine. We were brought up to believe that carbohydrates were the major fuel and that fat was burned only under exceptional circumstances.

The probabilities are that the reverse is true. If so, it means that a large amount of fatty acid must be transported throughout the twenty-four hours, and transported in an aqueous medium. Two problems arise, because fat and water do not mix. One concerns transportation and the other solubilization. As Dr. Sperry has indicated, the major function of the protein part of the lipoproteins is solubilization. One can say, then, that many facets of the transport problem are tied in with the other lipid components of plasma.

To refresh the memories of those who have not been thinking about fatty acids recently, most of the fatty acids found in the blood stream belong to the relatively long-chain acids with 16 or 18 carbon atoms. They vary from fatty acids with no double bonds to those with 1, 2, 3, 4, and even more double bonds. Assuming that the spacing is right in a geographical sense, any fatty acid with 2 or more double bonds is an essential fatty acid. One with only 1 double bond acid (*e.g.*, oleic acid) is a nonessential fatty acid, since it can be made from carbohydrate and other things. Linoleic acid has 2 double bonds. Linolenic acid has 3 double bonds and may or may not be essential. Arachidonic acid with 4 double bonds is in the essential group. The question arises, "What do we mean by *essential* and what has this to do with some of the clinical aspects in which we are interested?"

If the task is to transport fatty acid in an aqueous medium and keep the machinery from "gumming up" in the process, there must be a transport system. To turn now from reasonably factual information to the hypothetical, we conceive of the glycerides as being the main source of saturated fatty acids (which are the fuel fatty acids), and of the phospholipids as being the acceptor and the metabolically active transporter. Cholesterol esters concentrate essential fatty acids and pass them on to lecithin as required. In order to keep this whole system in balance, there must be an adequate amount of the polyunsaturated fatty acids in order to form normal lecithin, which in turn transports the saturated fat for energy purposes. If there is a shortage of essential fatty acids, then there may be an increased rate of synthesis of fatty acids and of both the phospholipid and cholesterol. Thus the blood levels rise and abnormal deposition can occur. This is only a working hypotheses, but at least it is something to stimulate a little thinking, and it is subject to experimental approach.

Recently, there has been a tendency on the part of some people who a little

while ago were saying that fats were fats, that all of them were "bad" and that there was no difference between one kind of fat and another, to go completely to the other extreme and come out with formulae that tell exactly how to select fats if one desires a certain blood level of cholesterol.

DR. SPERRY: May I amend what I said a few minutes ago. You reminded me of a major omission. When I listed the types of lipids in the blood serum, I overlooked an important one discovered within the last few years, that is, fatty acids themselves—so-called nonesterified fatty acids that are carried in combination with albumin. This is exceedingly important in connection with fat transport. The evidence available leads me to think that fatty acids destined for use in combustion are carried partially, if not entirely, in that form.

MODERATOR KINSELL: Do you mean as the final step before they are delivered to the point of combustion?

DR. SPERRY: Apparently so. Of course, there is much to be learned.

MODERATOR KINSELL: Do any other members of the panel have any comments at this point, or shall we proceed to lay more ground work?

DR. WILKINSON: I warned that if you used the word essential I would contradict you. The so-called fatty acids have been proved to be essential only in growing rats, and in adult rats in a state of negative nitrogen balance. It is unwise at this point to call them essential. In the amount in which they are used to obtain any result, they are different from other essential elements of the body. One might just as well call whiskey essential as to call these fatty acids essential with the present state of our knowledge.

MODERATOR KINSELL: There is ample room to question this. Dr. Sperry, do you have any comments?

DR. SPERRY: I take mild issue with my colleague. Dr. Hansen has spent a lifetime studying essential fatty-acid deficiencies in human beings. He has amassed considerable evidence that they do occur. Can you interpret his findings?

DR. WILKINSON: Yes, sir, I think I can. Essential fatty-acid deficiencies in rats are quite different from so-called essential fatty-acid deficiencies in human beings. There can be protein deficiencies in human beings. There can also be essential amino-acid deficiencies. With our present knowledge, we cannot classify these fatty acids as essential in the same way that amino acids are. When a deficiency exists, it is in the intake of total fat, or maybe of unsaturated fat, but not of "essential" fat in the sense that we usually think of as metabolically essential.

MODERATOR KINSELL: Are there any other comments on essentiality?

As for the amount concept, I would suggest that this is not necessarily important. There is a tremendous difference in amount between the requirement of vitamin B_{12} and that of nicotinic acid. The amount of essential amino acids required is of vast magnitude compared to the amounts of other vitamins.

Essentiality, at least in my book at the moment, is purely a question of whether a substance is something you need but cannot make. I know of no evidence to suggest that linoleic acid can be made by human beings in any appreciable quantity.

The next topics are hyperlipemia and hypercholesterolemia. These terms have

been used rather loosely. I suspect many of us are less than totally clear as to what is meant by them. The panelists should at least have some ideas. Dr. Wilkinson, will you commence this discussion?

DR. WILKINSON: My group defines hypercholesteremia as an increase in the concentration of cholesterol and phospholipid only. On the other hand, hyperlipemia is a primary increase in the concentration of triglyceride with a secondary increase in cholesterol and phospholipid levels. I am certain that somebody here will disagree with that. However, when I talk about hypercholesteremia and hyperlipemia, you will know what I mean.

MODERATOR KINSELL: Dr. Graef, what thoughts have you about hyperlipemia and hypercholesteremia? We have previously agreed that one can have physical and chemical hyperlipemia. Does that still seem reasonable?

DR. GRAEF: Yes, I think it is reasonable. I also think it desirable to keep in mind that these are average normal values based upon an adjusted dietary and metabolic response to food intake and utilization which changes from time to time through the influence of many factors—not only the composition of the diet, but metabolic activity, hormonal action, storage phenomena, and the presence of disease, latent or overt.

Perhaps lipemia ought to be defined first. Is the blood normally lipemic? We might remind ourselves that a newborn child has a blood cholesterol level far below what we would regard as an average normal value. The level rises rapidly with the changing dietary regimen, and exogenous fat becomes a regular contributor. However, there are other factors in the adaptation which determine whether or not this blood is lipemic, and also determine the point at which it becomes hypercholesteremic.

MODERATOR KINSELL: The plasma in the fasting state is fairly clear in the normal person. In some people with abnormalities, it may look like milk. In normal people, at two to six hours after eating (depending upon the nature of the meal), it may be quite cloudy. Dr. Kark, have you any thoughts as to what all of this may mean in relation to any part of, or the whole, picture?

DR. KARK: The changes in the opalescence of the serum represent only a transport mechanism. The solubility of triglyceride depends to a large degree upon the presence of various factors like lipoprotein lipase and phospholipids. A serum can be quite clear and yet be hyperlipemic because of the presence of phospholipids. Gross examination of the serum will not tell the physician much about the lipid content, that is, the different kinds of lipids that are present. If the serum is distinctly creamy and milky, it represents hyperlipemia. Dr. Wilkinson is one of the people in this country who has made a thorough study of hyperlipemia and its treatment. Perhaps he would like to say something about it.

DR. WILKINSON: Although one can have a lipemic or hyperlipemic serum without lactescence—by lactescence I mean a detectable light-scattering effect—there is a great difference between detectable lactescence and creamy serum. One thing that we are particularly interested in is familial hyperlipemia, a condition in which the defect is the delayed removal of fat from the blood stream after a fat load. This lipemia may be detected; usually around the time a man is

25 to 35 years of age, his serum will begin to exhibit lactescence, because the slow removal rate means that the postprandial lipemia or hyperlipemia never returns to the fasting level before the next fat meal is added. Over a period of years, the lipemia increases in steplike increments. It is an addition process. Hyperlipemia may not be visible in a specific serum specimen, but if the patient continues to have hyperlipemia long enough, the point will be reached where some cloudiness can be detected in the serum.

MODERATOR KINSELL: Dr. Sperry, have you any further comments?

DR. SPERRY: I have many comments, but I hesitate to start. This question of lipemia and hypercholesteremia is one in which I have been much interested. The word lipemia simply means lipids in the blood. The question is, what is hypercholesteremia? Where is one to draw a line?

Many years ago, I obtained evidence that each person tends to maintain a level of cholesterol characteristic for himself. In fact, I ventured to call it a constitutional level. Several other people have obtained evidence in accord with that point of view. Therefore, what is hypercholesteremia for one person may be a perfectly normal—I hesitate to use the word—cholesterol level for another person, in accord with the particular concentration that he inherited. It is extremely difficult to define hypercholesteremia. I am inclined to be suspicious of values over 300 mg. per 100 ml. as indicative of hyperlipemia. I should like to ask Dr. Wilkinson where he draws the line. How does he decide what is hypercholesteremia and what is hyperlipemia.

DR. WILKINSON: We think that we have reasonably good evidence, on the basis of genetics studies, that there are roughly 3 ranges of cholesterol concentration. These may be considered either normal or abnormal, but they are genetically determined. If it had not been for the Liebermann-Burchard reaction and Dr. Sperry making the determination of cholesterols so easy, we might have had less interest in this particular lipid.

Using the Sperry-Webb method of determining cholesterol, values up to 210 mg. per 100 ml. are considered to represent normal cholesteremia; that is, the person has no inherited trait of hypercholesteremia. From that level up to 400 or 450 per 100 ml. is indicative of heterozygous hypercholesteremia.

We see fluctuations in each of these groups. Unfortunately, overlapping occurs, particularly between normal cholesteremia and heterozygous hypercholesteremia. There is probably an overlap of 30 or 40 mg. Usually, however, one can be sure of the genetic determination corresponding to a given level.

DR. SPERRY: I should like to introduce the question of age, which, after all, is the subject of this discussion. For many years I thought that the cholesterol level was established within the first year of life and stayed there throughout. However, Ancel Keys has produced an imposing body of evidence on nearly 1500 persons which shows that the average concentration rises in a fairly steep curve up to about the age of 55 years, and then drops in old age. I should like to ask Dr. Wilkinson whether or not he takes the age factor into account in setting these different ranges. What are his comments on the age factor?

DR. WILKINSON: I can answer better three months from now. You may be

interested to know that we have secured a grant to restudy a hypercholesteremic family of about 300 people. That will be a 10-year checkup. I do not say that my opinions will be the same in three months, but the results will be published no matter what we find.

We have thought, up to now, that the increase of the cholesterol level with age is not as large as Dr. Keys has reported. Many factors must be considered when cholesterol concentration is determined at random. For instance, it is unfair to compare people who have just had a coronary thrombosis, or who once had a coronary thrombosis, with people who have had none. Atherosclerosis may be present in both groups. The only way to determine the effect of these various factors on disease, and that is what we are talking about, is to compare them within specific genetic groups.

For instance, in the large family in Michigan on whom we reported about ten years ago, considerable hypercholesteremia exists. I am talking about the heterozygous, not the homozygous type. Many of the people in this family have what we would call normal cholesterol levels. However, there is little coronary heart disease. In another large family in Connecticut that we are studying, there appears to be a great deal of coronary heart disease, both in persons with normal cholesterol levels and in those with hypercholesteremia.

In the Michigan family, the incidence of coronary disease in hypercholesteremic persons is far lower than among the general population. It appears from the data thus far assembled—we have not actually finished this study, but we have enough to believe that we can speak with some assurance—that the incidence of coronary disease among the persons with normal cholesteremia, in this one family in Connecticut, is greater than among the general population. Thus, if we just collect people at random and measure their cholesterol levels, I am afraid we may be misled.

MODERATOR KINSELL: Dr. Sperry, did you have something to say?

DR. SPERRY: I was glad to hear Dr. Wilkinson say that his data did not entirely agree with those of Dr. Keys. Did I hear you correctly?

DR. WILKINSON: That is what I said, but I also said that we are going to restudy this group. This will permit us to compare the cholesterol levels in the same people after ten years.

DR. SPERRY: We entered this field, too, after Keys presented his data, and decided to re-analyze the group that we studied thirteen to fifteen years earlier. Although we found a small average elevation in cholesterol concentration in the majority of the men in our little group (there were not enough to justify any conclusion), the increase was not significant. In fact, in some of the men, the level had dropped. Peterson and Man found the same thing. In a group of persons in whom they had determined cholesterol levels seventeen to nineteen years before, there was an insignificant change of only about 0.6 mg. per 100 ml. on the average; some levels had risen and some had declined. In several other studies reported in the literature, there was no drop in old age. This will require much study. The point I want to make is that Keys may well be right as to the average picture—one cannot very well dispute results in 1500 persons—but it does

not necessarily represent what happens in every person. There is a wide individual variation in the cholesterol level of the blood serum.

DR. WILKINSON: That is perfectly correct. Another thing that has to be pointed out is that only recently have people attempted to distinguish between hypercholesteremia as a primary thing—I am speaking about the inheritance form or central familial hypercholesteremia—and the hypercholesteremia that is secondary to hyperlipemia. If one were able to obtain the raw data of many of these studies, it would be found that many of these people were hyperlipemic, and one would expect an increasing concentration of cholesterol in the blood. Lipemia increases in step-like increments and elevation of the cholesterol level follows. Thus, when large groups of persons are tested only for cholesterol, one may be misled. I should like to hear Dr. Sperry's comment.

DR. SPERRY: I have no comment other than what I have just said. One can well be misled, it is true. There is a wide individual variation. For this reason, I have practically refused to use the word normal in connection with cholesterol concentration, although I suppose one has to use it.

MODERATOR KINSELL: Apparently the members of this panel are in thorough accord at this moment. Is that so, or does someone think that he is in a position to talk about a normal level of cholesterol or a normal level of phospholipid?

DR. WILKINSON: If you can give me another genetic term to use besides normal, we can separate cholesterol values into 3 groups. I shall be glad to use another term. We have interpreted the normal cholesterol level to mean the absence of an inherited trait which would increase cholesterol concentration.

MODERATOR KINSELL: If we do not know the normal range, it would seem that we are not in a position to define the abnormal, or to indulge in any philosophy about any kind of diagnostic test that may indicate precisely the state of the coronary arteries.

Cholesterol in the diet has received much attention for many years. We are overworking Dr. SPERRY, but he has so much to offer in this field that I hope he does not mind. Do you have any thoughts about dietary cholesterol?

DR. SPERRY: Yes, I do. I can be positive about this, on the basis of available evidence. In fact, I can be categorical. I know of no evidence that there is any relation between the cholesterol level in the diet and the cholesterol concentration in the blood serum of human beings. In animals, different dietary effects can be obtained.

Many years ago, we performed a series of experiments in which we fed a breakfast rich in cholesterol. The control subjects had no breakfast. We followed the serum cholesterol level for several hours. There was no difference. Nothing happened. Those were short-term experiments. Others have carried out similar studies. Recently, there have been more elaborate surveys, that of Keys probably being the largest. I think Dr. Wilkinson has carried out such a survey. The result was that there was no relation at all between the level of cholesterol in the diet and the concentration in the blood serum. Do you agree with that, Dr. Wilkinson?

DR. WILKINSON: Yes, I certainly do, with one exception. That is the work of Murray Steel. If one considers as cholesterol, the equivalent of as many as 28 eggs

per day added as dry egg yolk to a normal diet, a measurable elevation in blood cholesterol concentration can be obtained. Such elevations are not clinically significant, however. This is the only work I know wherein the blood cholesterol level has been increased by the addition of cholesterol to the diet. Bear in mind that Dr. Steel could do this only with dried egg powder. He could not do it with the same amount of cholesterol dissolved in lecithin, nor with the same amount of cholesterol dissolved in anything else.

MODERATOR KINSELL: Perhaps we should now discuss blood vessels. Dr. Graef, will you tell us some of your ideas with regard to atherosclerosis?

DR. GRAEF: I want to be careful on semantic grounds lest we continue to operate in a self-made trap. Arteriosclerosis has been referred to aptly as an omnibus term, a catch-all, for changes in blood vessels which may or may not have significance for the patient. It includes a variety of changes that may begin in the intima, in the media, in the adventitia, or in all three layers at once.

Included under arteriosclerosis are the recognizable disorders of the blood vessels—those associated with lipid deposits, those associated with calcific deposits, and those in which there is only necrosis in the media. Complications include overlaps due to the presence of more than one material.

I should like to emphasize what we do not know about *atherosclerosis*. In trying to say what we do not know, I shall touch upon a few of the things that we have learned throughout the years.

Atherosclerosis may be defined as a disorder of the blood vessels, especially of the arteries. By arteries, I mean the elastic-tissue arteries—those with an internal elastic lamella and external elastic fibers. The arteries in atherosclerosis undergo a change associated with the deposit of material that is first seen as an intracellular aggregation of composite lipids. There is evidence that these lipids tend to mirror, but not exactly, the lipids in the circulating blood. They gain entrance into the intima through changes in the endothelium, and tend to accumulate in the ground substance in a spotty, rather unpredictable distribution pattern.

In man, arteriosclerosis associated with atheroma formation includes the aorta as well as the medium-sized elastified arteries. These lesions lead to dire consequences in organs that have a limited collateral blood supply, and when associated with occlusive phenomena are the harbingers of catastrophe because of the impact of reduced blood flow on the organ served by these arteries. The effects in an organ like the heart are greater than in other organs because of lack of alternate or reserve cardiac capacity in dealing with changes in nutrition. Yet the tolerance in any given organ is extremely unpredictable. Silent injury is common; in 20 per cent of myocardial infarcts found post mortem, there was no clinical record of the disease prior to death. There may be no correlation between the degree of occlusive disease and the clinical effects. It is common to refer to coronary artery disease as coronary thrombosis, yet all necropsy data indicate that between a quarter and a third of patients with myocardial infarction do not have thrombosis but merely atherosclerotic narrowing of the coronary arteries.

Recent careful studies have shown that there may be no correlation between the coronary involvement and similar lesions in other arteries of the body, with

the possible exception of aortic atherosclerosis. Fortunately the aortic lesion is seldom associated with severe local changes.

As to the plaques in atherosclerosis, they vary considerably at different stages. The earliest lesion is an intracellular aggregation of lipids tending to mirror those of the blood stream, but dominated principally by cholesterol in the form of droplets combined with a certain amount of triglyceride. As the lesion increases in size, the lipid tends to become extracellular and the esters form in masses, which then become cholesterol crystals. These insoluble substances probably cannot be moved by any means we now possess. In considering the prevention of atherosclerosis, let us face the fact that we are concerned with years of accumulation of this material. The problem involves much more than the reversal of a plaque associated with an occlusive phenomenon.

The reversal of experimental lesions can be demonstrated, as long as the lipids are intracellular. I know of no experimental evidence to show that the extracellular deposits can be mobilized with any readiness. This problem has to be tackled.

MODERATOR KINSELL: One classifies aging into two major brackets, namely, physiologic and pathologic. Physiologic aging is the time-clock sort of thing that is based on the general concept that none of us will live forever, and on the further concept that, barring intercurrent disease of major magnitude, one can live to an advanced age and finally die suddenly—a one-horse show phenomenon. Pathologic aging, on the other hand, involves changes that are not part of the time-clock mechanism and which may interfere with functional capacity, particularly mental functional capacity. To my mind, fatal coronary occlusion, although disturbing and dramatic, is not as disturbing as the changes in the cerebral vessels associated with vegetative changes that occur in previously productive members of the community. Atherosclerosis is a tremendously important public health problem as well as a personal and medical problem. Its clarification is worth all the effort we can put into it. In line with what Dr. Graef just said, would you put atherosclerosis in the physiologic or in the pathologic category? Do you think that, if one lives long enough, atherosclerosis will inevitably develop, or do you think that it will be totally preventable when we know the right answers?

DR. GRAEF: I believe that it is preventable. I think that atherosclerosis is a disease of man, his environment, and his diet.

MODERATOR KINSELL: Do any of the other members of the panel think otherwise?

DR. SPERRY: I think I heard Dr. Graef say that there was not necessarily a correlation between coronary involvement and atherosclerosis of other arteries. Over twenty years ago, Landé and I measured the degree of atherosclerosis in the aorta and the cholesterol concentration of the serum in a fairly large number of persons who had died sudden deaths. We found no relation whatsoever. I hesitated to mention this. I am back to cholesterol again, because all of the interest in cholesterol in relation to this problem has come from the fact that there is a relation between blood cholesterol concentration and coronary disease.

It is not a very strong correlation, but it is statistically significant. Our studies showed that there was no relationship between serum cholesterol concentration and the degree of atherosclerosis in the aorta. Later, Faber in Scandinavia obtained the same result. These findings have been ignored, but recently Patterson, Cornish and Armstrong in London, Ontario, attacked the problem in a different way. They took samples of blood from persons in veterans' hospitals at yearly intervals and preserved them frozen. After some of the subjects had died, they carefully evaluated the degree of atherosclerosis and determined the cholesterol content of the preserved blood samples along with some other things. In 50 subjects so far, they have found no correlation between the 2 variables. From these results, I doubt that there is a close correlation, if any, between the serum cholesterol level that we are worrying so much about and the degree of generalized atherosclerosis, if that be the correct term. I heard recently that there is no correlation between the serum cholesterol level and cerebral atherosclerosis.

DR. WILKINSON: It would be unfortunate to think of atherosclerosis as *not* the same thing as coronary artery disease. Let us take atherosclerosis itself. There is a good reason to think that 2 types of factors affect it—primary and secondary. Among the primary factors is trauma. The blood vessels are subject to trauma, for instance at a bifurcation of the aorta or in the heart muscle where there are different types of support before and after the vessel plunges into the muscle. It is at these points that plaques usually form. It is a continuous process, but it is also sporadic. Trauma alone will not account for the fact that this is a sporadic disease. Thus, we have to postulate the secondary factors. In my opinion, hypertension is probably the most important secondary factor known today. I would agree with Dr. Sperry that, if hypercholesteremia be a secondary factor, it is way down on the list.

MODERATOR KINSELL: We all agree, apparently that atherosclerosis is potentially a preventable disease. We would probably agree also that nobody thinks that he has the answer to prevention. This does not mean that there are not pieces of information that may bear strongly on the subject. Instead of discussing this in terms of a specific consideration of procedure A, B or C, I wonder if we might now resort to questions from the audience with the thought that some of you may have specific questions that will help us to supply information.

SPEAKER FROM THE FLOOR: I have a question for Dr. Wilkinson concerning the clearance of the blood during a fatty meal. You stated that, in persons with hyperlipemia or hypercholesteremia, the serum levels never return to normal following a fatty meal because they do not clear rapidly enough. Will you comment upon the advisability of a fat-free breakfast which would provide a period of sixteen to seventeen hours, from the night meal until approximately noon the following day, in which the blood has a chance to clear?

Dr. Sperry said that he does not like to use the word normal, although he did use it when he said that what is normal in one person might be considered hypercholesteremia in another. That still does not comment on the question of whether this is the normal level. It is an optimum level for the person concerned. It may be normal for him, but is it an indication of a healthy person?

I have 2 questions for the panel as a whole. The first deals with the whole

concept of normality as it may be considered with relation to the incidence of coronary heart disease. That would bring to mind the cooperative study on metabolism recently made and recorded, in which various ranges of serum cholesterol concentration were related to various rates for coronary heart disease. I believe that with cholesterol levels over 220–240 mg. per 100 ml. the rate for coronary disease was three times higher than when the cholesterol level was below 200 mg. Might we not get some concept of normality on a basis such as this? The other question is, why is it that with a fat-free diet or a low-fat diet that has been continued for a long period of time, a lowering of the blood cholesterol level will be obtained that is approximately equal in magnitude to that obtained by using a diet supplemented with unsaturated fatty acids for a shorter period of time? Let me rephrase that: When a person has been taking a fat-free diet for a long time, and his diet is then saturated or supplemented by unsaturated fats, why is there no further decrease in the blood cholesterol level?

DR. WILKINSON: The fat tolerance test, which I am not recommending, is a research procedure and costs too much to be practical for the average patient. We do not believe that it is necessary. However, in the fat tolerance test, the usual young person will clear the increased fat in six hours or less. The familial hyperlipemic person exhibits a measurable slowness, and usually takes sixteen and sometimes as long as twenty hours. In several cases, over twenty-eight hours has been required.

For many hyperlipemic persons, a fat-free breakfast is sufficient. I think you are referring to the published report. The reason we recommended a fat-free breakfast and a fat-free lunch was that by this method practically all of them could be controlled. After control has been secured on 2 fat-free meals a day, it is perfectly logical to add fat at lunch. This is not a restriction of the amount of fat eaten; it is merely a spacing of it. Also, as people grow old, they tend to have a prolonged clearance time. It does not become as long as in hyperlipemic persons. For the elderly patient, we recommend a fat-free breakfast for this reason; the atheromatous lesion is usually a mixed one, and parts of it may be reversible.

DR. SPERRY: I can best answer the question concerning normal cholesterol levels in terms of a specific case. For many years, Dr. Bela Schick and I studied a patient with severe xanthomatosis. The serum cholesterol level was elevated to 700 or 800 mg. per 100 ml. The patient came from a family similar to the one to which Dr. Wilkinson referred, except that this one was much smaller as far as we studied it. The father and mother both had hypercholesteremia with levels over 400 mg. per 100 ml. Two brothers also had hypercholesteremia. We followed them for years. The mother and one of the brothers consistently showed values of 400 to 500 mg. per 100 ml. and over, although they were perfectly healthy. The brother was in the Army. Physical tests showed nothing wrong, but the mother eventually had a coronary thrombosis. My point is that these cholesterol values were inherited. In that sense, they were the normal values for these people. I do not mean to imply that they are optimal values; quite the contrary. In other words, I agree with Dr. Wilkinson's type of classification. The values are normal in a sense, but not optimal.

MODERATOR KINSELL: I would strongly question that with a low-fat regimen

as compared to a properly constructed diet high in unsaturated fat, one can obtain anything like the same quantitative or qualitative picture. What is the significance of lowering the blood level of cholesterol? The blood sugar level in diabetes can be lowered by giving insulin, by giving phloridzin which will let the sugar run out in the urine, or by poisoning the liver. No one would say that these are equally desirable or similar procedures, but they have in common the lowering of the blood sugar level. This is the stage we are in with cholesterol at the moment.

SPEAKER FROM THE FLOOR: May I ask the panel a question? Proteolipids and lipoproteins were mentioned. What about the disease, liponephrosis? Is this disease or syndrome still considered to be due to a disturbance in fat metabolism, or is it in protein metabolism, especially in the old age group? We used to see pronounced protein metabolic disturbances, for instance, reversed serum albumin /globulin ratios.

MODERATOR KINSELL: Dr. Pollack, would you like to comment on that?

DR. POLLACK: The attempt to explain everything on a unitarian basis is one of the reasons why we so frequently run into difficulty. The observations on hyperlipemia in nephrosis are well known. Whether the hyperlipemia is secondary to protein disturbance is still subject to investigation. The possibilities are that there is a direct relation. We must not forget, for instance, that we are dealing with a complete inter-relation in all of this discussion of atherosclerosis and arteriosclerosis, and hyperlipemia and cholesterol. Nobody has mentioned the classic disease, diabetes. In the diabetic patient, we see the onset of atherosclerosis and arteriosclerosis at a much earlier age and at a much more rapid rate of progression than in the nondiabetic subject.

We know from the discussions of Dr. Graef and Dr. Allison that we are dealing with certain inter-relations among carbohydrates, proteins and fats. We discussed anabolic hormones, but we did not mention the fact that insulin is probably the most potent of all the available anabolic hormones.

We discussed osteoporosis and atherosclerosis. The postmenopausal female is most subject to osteoporosis, and the atherosclerotic female is most subject to diabetes. For the sake of being provocative, I should like to throw open again this whole question of the place of insulin in the present status of atherosclerosis and vascular degeneration.

MODERATOR KINSELL: As a member of the panel who has used a good deal of insulin, what would be your comments on that, Dr. Graef?

DR. GRAEF: Before exogenous insulin was available, the observations that Dr. Pollack made were just as cogent. The diabetic patient today lives to mirror the associated lipid disturbances that accompany his inability to utilize carbohydrate efficiently, or in the manner of an efficient nondiabetic.

It is a very provocative matter. The disturbances associated with abnormalities in the levels of all the lipid fractions so far measured are much worse in uncontrolled diabetes than in controlled diabetes. Vascular changes occur even in the best controlled diabetic patients, but abnormalities in the levels and ratios of lipids and total cholesterol, in the distribution of abnormal high-density lipoproteins, and in the metabolism of both esterified and nonesterified fatty acids,

characterize diabetes. In this disorder we are dealing with complex changes that affect the distribution of these lipids. These in turn are associated with vascular lesions that make a great deal of difference in the life expectancy of the patient, regardless of whether the coronary component, the retinal component or the renal component predominates.

So far, the experimental animal has not yielded information comparable to that which nature provides for us in the diabetic subject. I do not know what role insulin plays in vascular lesions, but I would remind you that insulin acts on depot fat as well as on depot glycogen and glucose in the muscle.

MODERATOR KINSELL: I should like to ask Dr. Sperry to give any final thoughts he may have with regard to nephrosis.

DR. SPERRY: I have nothing really worthwhile. I left Babies' Hospital in 1938. While I was there, I studied a number of patients with nephrosis and was amazed at the extremely high levels of serum cholesterol. I was even more amazed to find that the proportion of free cholesterol to esterified cholesterol was within the narrow range that one sees in normal persons. Why the cholesterol level is elevated, the nature of the mechanism, the relation to the disturbance of proteins, and whether it is all related to lesions in the kidney, I cannot answer. I do know that there are profound disturbances.[1]

DR. ALLISON: In the experimental animal, we can alter the cholesterol and phospholipid content of plasma by altering the physiologic state of the animal, particularly by alterations that affect protein metabolism. The data demonstrate that there is an inter-relation between the various metabolic processes involving protein and fat metabolism and the development of hypercholesterolemia.

MODERATOR KINSELL: I thank each member of the panel. That ends our discussion.

[1] Since I made the reply, it has been suggested that the disturbance in lipid metabolism in nephrosis results from the decreased concentration of serum albumin which, in turn, makes normal transport of unesterified fatty acids impossible.

EXAMINATION OF AN ELECTROCARDIOGRAM*

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An electrocardiogram can be properly evaluated only if it can be inspected as an integrated entity. The method of taking, mounting, and reading the electrocardiogram has come down to us from the time of Einthoven's original contribution of the standard limb leads in 1902. It has been an evolutionary process, similar to that involving our old highway system, which through the years has been developed into a modern dual freeway system with correlated exits and entrances in proper relation to the main strips of roadway.

The visiting physician on a medical service, the interne, or the resident may be in a quandary as to what the electrocardiogram reveals, if the report of the cardiologist is not yet in the folder. The limb leads are on one section of the chart, the precordial leads on another, and the aVR, aVL and aVF in various positions. He vaguely remembers something about a Q3T3 pattern, but does he look for help in the aVR, the aVL, or the aVF? It is important to determine the significance of prominent Q or inverted T waves in leads 1 and 3. These can be due either to the position of the heart or to myocardial damage, especially in posterior infarction, because the diaphragmatic surface of the heart is viewed in the left-leg lead aVF more definitely than in the bipolar limb leads or unipolar precordial leads (1). Where does one look for the upright R in the unipolar precordial leads in order to obtain corroboratory evidence of right bundle-branch block, and is the same R wave seen in right ventricular hypertrophy? (2). Similarly, in which precordial leads does one look for the absent Q, depressed S-T, and upright T for corroboratory evidence of posterior infarction?

Although the first published electrocardiogram (Waller, 1887) represented a chest lead, convenience and chance led early electrocardiographers away from the thorax itself toward limb connections, and only in later years has there been a return to the precordium as an important focus of attention. (3). The method of taking, mounting and reading the segmented strips of the electrocardiogram was limited to the 3 bipolar limb leads of Einthoven; the recordings were placed beneath each other and studied for differentiation of the arrhythmias. As a result of the early work of Wilson and his colleagues and of Wolfreth and Wood, precordial electrocardiography was introduced into clinical medicine. (4). The CF2 and CF4 were placed under the 3 bipolar leads of Einthoven and much confirmatory information was ascertained in the diagnosis of anterior and posterior infarction of the ventricles (5). Then came the 6 precordial leads of Wilson; the recordings were placed on another page, and the aVR, aVL and aVF were placed laterally to each other between the limb leads and the precordial leads. We continue to register the bipolar limb leads be-

* With assistance from the Sanborn Company, Cambridge, Mass.

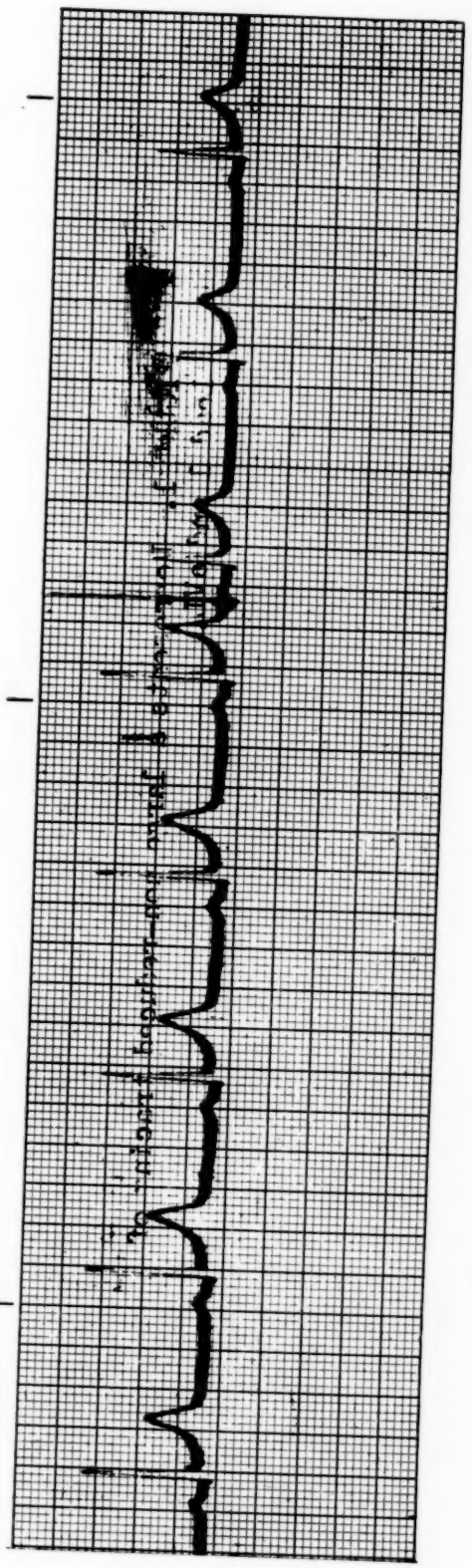

FIG. 1. Electrocardiographic tracing of lead 1 and aVL

cause of familiarity and the fact that they represent the mechanisms of tachycardia and bradycardia; we record the arrhythmias because they have become a part of the patterns established in acute cor pulmonale, congenital atrial septal defect, advanced mitral stenosis, and chronic constrictive pericarditis involving the left chamber of the heart. Since 1951 the use of the unipolar limb

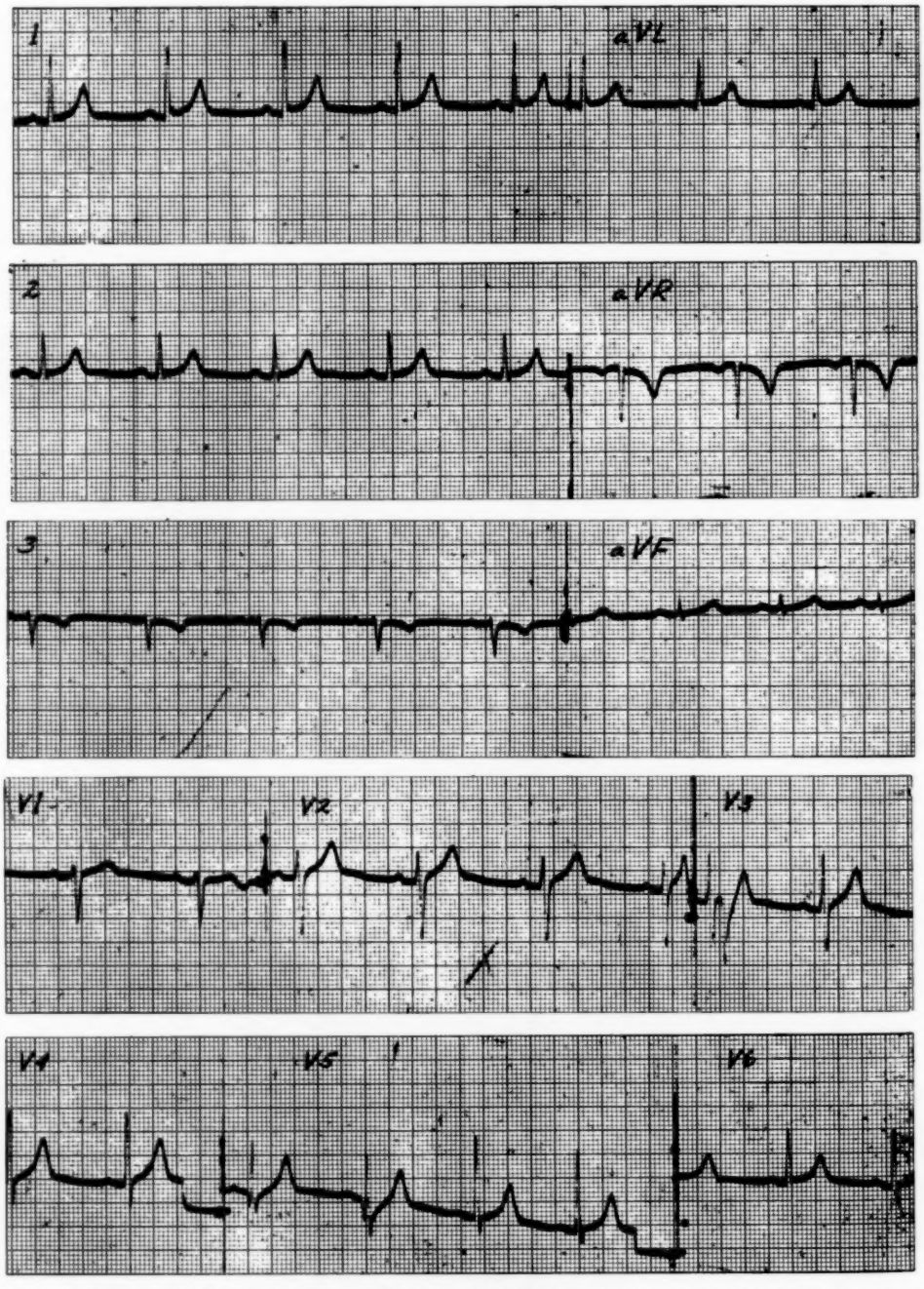

FIG. 2. Entire electrocardiogram. The inverted T in lead 3 is not significant because aVF shows an upright T in the same lead.

leads, aVR, aVL and aVF has apparently become practically universal, either to replace or to supplement the bipolar leads (6).

PROCEDURE

Sequence of leads

A 12-lead tracing is mounted on one page measuring 8 by 11 inches, the standard limb leads are correlated with the unipolar limb leads (*i.e.*, lead 1 with aVL, lead 2 with aVR, and lead 3 with aVF; V leads 1, 2 and 3 as a group; and V leads 4, 5 and 6 as another group) in order to orient the recorder and the reader with the simultaneous relationships of the tracings, to make interpretations easier, and to facilitate the process of mounting. To eliminate the bulk that accumulates when serial tracings are taken, and to simplify the work in looking up records for statistical study, the following technique is used for any direct writing machine. The subject is in the sitting position. This cuts down the space occupied in a small examining cubicle, is easier on obese, elderly, and dyspneic patient, lessens somatic tremor, and is particularly valuable for eliciting abnormal Q waves in leads 2, 3, and aVF (7).

The lead selector is turned to lead 1, and if the rate is 70 per minute, six complexes (14 mm.) are recorded with the usual standardization. The lead selector is now advanced to aVL, and four complexes (7 mm.) are recorded. Use of the lead marker to code each lead and for the end of each strip will facilitate the later procedure of mounting. The lead switch is then turned back or counter-clockwise to lead 2, and six complexes (14 mm.) are recorded; next the switch is advanced to aVR, and four complexes (7 mm.) are recorded. The lead selector is now turned back to lead 3 and six complexes (14 mm.) recorded, then advanced to a VF and four complexes (7 mm.) recorded. The unipolar precordial leads are taken in 2 series: in the first row, V 1 with five complexes (8 mm.), V 2 with four complexes (7 mm.) and V 3 with five complexes (8 mm.); in the second row the same order is maintained for V 4, V 5 and V 6, which allows for the trimming of both ends if need be, for mounting.

Mounting

The first strip, which includes lead 1 with aVL, is cut off in one piece and stapled across the top of an eight-inch sheet, card, or folder (Fig. 1). Lead 2 with its corresponding aVR is next cut off and mounted under lead 1 and aVL. Lead 3 with its corresponding aVF is cut off in one strip and mounted under lead 2 with its aVR. The V leads 1, 2 and 3 are cut off in one strip and mounted under lead 3, and the remaining V 4, 5 and 6 leads are mounted under V 1, 2 and 3. The tracings are properly marked for identification and the electrocardiogram, now assembled on one page, is ready for interpretation (Fig. 2). If desired, proportionally shorter strips may be recorded, and each may be trimmed top and bottom for mounting on a sheet smaller than 8 x 11 inches.

INSPECTION

The mounted electrocardiogram now presents for examination 12 leads all on one page, showing the complementary relationship of the standard leads to the unipolar leads. The uppermost section presents lead 1 with its accompanying aVL. There is no question about where to look for corroboration of S-T segment change, T-wave inversion, or significant Q waves in lead 1, as aVL is placed on the same strip with lead 1. A questionable S in lead 1 in aVL will automatically indicate that a vertical position is present; and an R wave higher than 11 mm. in the same aVL will indicate a search for other corroboratory evidence of left ventricular hypertrophy.

Lead 2 is directly under lead 1 with its projection into aVR. The aVR is

the inverted mirror image of lead 2, and being a part of the strip of lead 2, a beginner cannot be confused and erroneously correlate the normally inverted T in aVR with a T inversion in leads 1 or 2. The mere finding of an upright R in aVR provides a clue in the recognition of right bundle-branch block or right ventricular hypertrophy. Myocardial anoxia usually results in depression of S-T segments in all the leads except aVR, where it is elevated and can readily be spotted in a lead that is normally inverted. In a study of 65 consecutive deaths of patients with abnormal electrocardiographic changes, it was found that 30 patients with no S-T segment changes in aVR had lived four to six years after the recording of the tracing. Thirty out of 35 who had S-T segment elevation in aVR died suddenly or within six months after recording of the tracing. Lead 3, with its twin magnified in aVF situated alongside it, will furnish the reader with any significant clues—Q waves, T inversion and S-T segment changes, either pathologic or benign.

Looking at the first row of the V leads Nos. 1 to 3, we normally expect to see an S wave. The mere presence of an upright R intruder will automatically indicate right ventricular hypertrophy, or right bundle-branch block if the QRS interval is prolonged, differentiating it from left bundle-branch block. The second row of V leads, Nos. 4 to 6, normally shows an upright R; a deep S wave indicates right ventricular hypertrophy and anterior infarction; a Q wave will confirm a suspicion of anterior infarction. Sokoloff's criterion is that the sum of the R in V 5 or V 6 plus the S in V 1 should be more than 35 mm. for further evidence of left ventricular hypertrophy. The arrangement as depicted will furnish the reader with automatic landmarks simply by their position on the chart, in the diagnosis of a sextet of conditions: left and right ventricular hypertrophy, left and right bundle-branch block, and anterior and posterior infarction.

SUMMARY

Examination of an electrocardiogram, and of its salient features that affect interpretation, is more readily accomplished if the several leads are so positioned on the mounting card or folder as to make their relationship obvious. A sequence of lead selection while making the test, and a method of mounting the tracing to accomplish this purpose are presented and discussed. When electrocardiographic records are so mounted, the diagnostic landmarks are more readily manifest to the reader than when they must be searched for in the conventional mounting pattern.

An auxiliary lead switch facilitates this procedure by changing the sequence of lead selection to lead 1 and aVL, lead 2 and aVR, and lead 3 and aVF, while maintaining the precordial leads in the usual position.

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THE TREATMENT OF SUBACUTE ASTHMA IN THE OLDER PATIENT

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This discussion of the treatment of subacute bronchial asthma in the older patient is only partially objective and otherwise personal and biased. The author believes that patients who suffer from bronchospasm should be relieved as quickly and as completely as possible and recurrences should not be permitted; thus the patients serve as their own "controls." The techniques described are the results of trial and error in studies conducted over a period of twenty years, and they have repeatedly been purified in the crucible of everyday practice. Theoretical considerations are given only brief mention, and only as they help support the basic concepts described.

Those of us who routinely examine the lungs, especially of the older asthmatic patient, often hear evidence of bronchospasm when the patient has just finished telling us that he is free of symptoms. Obversely, those of us who routinely perform pulmonary function studies frequently find ourselves faced with proof of bronchospasm when concomitant stethoscopic examination of the lungs leads us to believe that no spasm is audible. If neither the patient nor the physician can be certain of the presence of subacute bronchospasm, then our attitude toward the treatment of this disorder must change.

Asthmatic patients are evidently no different than are, for example, diabetic or hypertensive patients. In diabetes, the treatment does not depend upon what the patient says, but on the blood sugar levels. In hypertension, we go by the sphygmomanometer readings and other signs. Our goal in the treatment of such diseases is to prevent irreversible damage and eventual extension to other body systems. Asthmatic patients must be looked upon from exactly the same point of view.

At this juncture, it might be well to define the limits of our ignorance. We do not know why allergic patients are so specifically affected by such minute quantities of substances apparently harmless in great quantities to non-allergic subjects. We do not know why patients become allergic to one substance and not to another when exposure to both may have been equal. We do not know why, despite continued exposure, occasional long-lasting remissions occur; the infrequency of such remissions may be due to the fact that the patient is usually sensitive to only one allergen, the accidental or circumstantial elimination of which apparently frees him of bronchospasm.

We do know, however, that many older patients apparently in state of remission are asthmatic, although below the level of conscious dyspnea. We also know that asthma is not at any age "outgrown," because it is in no way related to the biologic processes known as growth. A patient is not allergic just

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because he presents the typical syndromes associated with allergy, but because he is "*allergic*," just as a diabetic patient is "diabetic" although his blood sugar level may be within normal limits and there is no glycosuria.

In the typical subacutely asthmatic patient there is usually a clinical sensitivity to one or more seasonal and to several environmental (often biologically related) allergens. In older persons, good, but not perfect results may be expected to follow conventional injection therapy for seasonal, *i.e.*, for pollen sensitivity. At the peak of the pollen seasons, many such patients experience some discomfort, which may be so mild as to require no symptomatic medication. Pulmonary function studies at such times will show that the timed vital capacity is below the patient's extraseasonal measurements.

In dealing with sensitivity to environmental allergens, the problem is more complex. The patient can diminish exposure to bedding, dust or molds, and eliminate feathers or household pets, but exposure of some degree occurs at the office or while visiting. When the level of clinical distress is reached, medicine is usually taken, not because it restores normal pulmonary function, but because it makes the patient less uncomfortable. The stethoscope proves that when such medicines are taken for symptomatic relief, some degree of bronchospasm usually persists long after the patient says that he feels better.

Wheezing may occur not only following exposure to inhalants, foods and drugs to which the patient may be sensitive, but also in association with respiratory-tract infection, exertion, laughter, anger, exposure to cold air, ingestion of iced water or foods, or the inspiration of irritating fumes and odors such as those due to paint, smoke or fuel oil. Any emotion, exhilarating or depressing, may cause bronchospasm, as may also non-allergic lung disease and heart disorders. Occasionally, bronchospasm occurs for no apparent reason. It can easily be demonstrated that many asthmatic patients can, by means of active repeated forceful expiration, induce bronchospasm and a typical asthmatic attack. Such bronchospasm can also be induced in many normal non-allergic, non-asthmatic subjects.

It is our hypothesis that the patient's lungs must be protected against all degrees of bronchospasm, when such spasm can be proved to be continuously or frequently present, even though initially unsuspected. In order to practice at this basic level, a timed vitalometer must be available. The geriatrician must also know the properties, methods of prescribing, and possible side-effects of certain groups of drugs.

Our program, embodying as it does a special point of view toward patients suffering from bronchospasm, is not to be regarded as a short cut in treatment. It is as necessary as it ever was to take a detailed history, to perform a meticulous physical examination, and to make thorough roentgenographic studies of the chest and sinuses. In older patients a "base line" electrocardiogram is mandatory. Environmental surveys must be made and, at first, diaries of food intake and symptoms must be kept. Skin tests, especially for the inhalant allergens, are indispensable, though in the older patient the results are not dependable.

PULMONARY FUNCTION STUDIES WITH THE TIMED VITALOMETER

Studies and treatment are usually concurrent. The vitalometer with a timing mechanism tells us how much air the patient can forcefully expire in each of the first three seconds. It is used as a measure of the patient's progress. Since the values can be determined with reproducible accuracy, they can be used as a criterion of progress, in the way an internist uses successive determinations of the blood pressure.

If a vitalometer with an attached timing mechanism is not available, the three-second reading and the total vital capacity can be measured with a standard vitalometer and a stop watch.

Following full inspiration, a cooperative intelligent patient who is being tested by an enthusiastic technician should be able to expire 95 per cent of his predicated normal vital capacity (as determined from easily procured printed tables). The arrow on the machine should, therefore, cease moving a fraction of a second after the three-second interval.

In patients with bronchospasm, the expiration time is prolonged beyond three seconds, up to ten seconds. Thus the timing is an important part of the test; total vital capacity unrelated to time may appear to be normal or even above normal.

In asthmatic patients, the forceful expiration called for by successive tests often causes bronchospasm. Consequently the amount of air expelled in each three-second period is reduced. With increased spasm, the total vital capacity also decreases, so that both readings are successively lower. This is a diagnostic point of great importance in proving the presence of true bronchial asthma.

A prolonged expiration time has been recorded in 10 to 20 per cent of persons not suffering from either bronchial asthma or subjective dyspnea. The test is therefore not an absolute criterion in the absence of a typical history and of other signs and symptoms.

If more refined diagnosis is desirable, the maximum breathing capacity can be determined. In subacute asthma or in subclinical bronchospasm, the patient's maximum breathing capacity is usually 60 to 80 per cent of the predicated normal value. Occasionally the total vital capacity is greater than the predicated normal value, with less than 95 per cent of this total expired in three seconds. An analysis of the ratio of the residual volume to total lung capacity shows it also to be greater than normal (almost double), indicating that older asthmatic patients usually also suffer from some degree of emphysema.

In emphysematous patients (some of whom are non-allergically asthmatic) the total vital capacity may be above normal, but the amount of air expired in three seconds and the total quantity moved in one minute are both decreased. When an occlusive lesion is present, it takes up space to the exclusion of a corresponding amount of air, and therefore the three-second reading will be low; the total vital capacity and the quantity moved in one minute will also be low. In the presence of restriction, however, though the quantity moved in three seconds will be low, the total vital capacity may be normal; the maximum

breathing capacity will be low because of the additional work involved in moving the inspired air and expired air.

TREATMENT

Types of mucus

Prophylactic and therapeutic medical treatment requires a knowledge of the nature of 3 types of pulmonary mucus, each of which is derived from a different portion of the respiratory tract.

At the alveolar level there is mucus of high viscosity, known to us only through refinements in the technique of bronchoscopy. This mucus is never coughed up as such. It is also undoubtedly present in any unaerated or hypoxic portion of the lung. Because of the fear of inducing an attack of bronchial asthma, many older asthmatic patients do not use their lungs either properly or effectively. They may, therefore, suffer from the presence of an excess of this type of mucus. The pulmonary cells excrete fluid into this mucus and then reabsorb the solid constituents. Bacteria affect it, as do enzymes such as mucinase. When it becomes dry, it may exist as the so-called "mucous plug." Either by ciliary action in the erect or by gravity in the prone position, small amounts of it may reach the region of the cough area. Expectorants can then decrease its viscosity and, by making it less tenacious, enable the patient to raise it. This mucus is, however, not usually affected by expectorant drugs taken orally, although they may be effective by the inhalational route when this leads to deepened inspiration and aeration.

Another type of mucus is the result of inflammation. It is seen when the pulmonary cells must wash out bacteria or neutralize the effects of bacterial toxins or noxious vapors.

The third type has been noted clinically and bronchoscopically during local or general allergic reactions when it literally pours out of the glands.

Drugs

Potassium iodide is the drug of first choice. The iodide ion is excreted by the bronchial glands within five to twenty minutes, but only at the free border of the bronchial and tracheal mucous membranes.

Potassium iodide usually acts, not by way of excretion into the lung, but because it is a specific irritant of the gastric mucous membrane. Part of its expectorant action is reflex. In clinical medicine, the less irritative protein-iodide compounds are the less effective expectorants. When gastric distress occurs it may be severe, and the patient may complain of pain. Administration of iodide may cause an ioderma and, rarely, arthralgias, urticaria and periarteritis nodosa. When the dosage is more than 5 grams daily, the formation of thyroid hormone may be blocked. If goiter should develop, recovery follows substitution of iodide therapy with desiccated thyroid, 120–200 mg. daily.

Potassium iodide must not be used in inflammatory disorders of the lungs, but in late bronchitis, bronchiectasis, and in older asthmatics it is an ideal therapeutic agent. For whatever reasons, some patients need no other prescription

in order to stay free of bronchospasm, which recurs when administration of iodide is discontinued.

The initial dosage is 0.3 Gm. every two hours, with lengthening of the interval as secretory effects become apparent.

If after one week the clinical course and results of pulmonary function tests indicate little or no response, the next step is the use of antispasmodic drugs.

Ephedrine will not increase the vital capacity of a normal subject. In asthmatic patients ephedrine improves the vital and respiratory capacities, lessens the volume of residual air, and moderately improves expiratory reserve volume. It is most effective in atopic asthma and is occasionally effective in the reflex type of bronchospasm. It is least useful when bronchospasm follows infection. It is superlative as a prophylactic medication for asthma.

Addiction to ephedrine occurs rarely, and equally rarely it may produce a dermatosis. In middle-aged males it may cause urinary retention, but the patient often can continue to use ephedrine if he remembers to empty his bladder before he takes each dose of the drug.

Care should be exercised in the routine use of ephedrine, since oral administration of doses of 50–400 mg. may raise the systolic pressure by as much as 30 mm. Hg for as long as five hours. If epinephrine must be administered for an attack of asthma, there may be a cumulative rise in blood pressure. However, bronchospasm may also raise the pulmonary and systemic blood pressures, so physicians need not concern themselves unduly with the hypertensive effects of the drug.

None of its isomers or analogues appear to act as well as ephedrine itself. When ephedrine does cause over-stimulation, racephedrine, which is less potent, may be substituted.

The clinical contraindications to ephedrine are nervous excitement, insomnia, tremors, an increase in anxiety, and (rarely) a sense of weakness. Ephedrine (25–50 mg.) is therefore usually administered with a sedative—either phenobarbital (30 mg.) or pentobarbital (25 mg.). It is usually prescribed with aminophylline or one of its analogues. One of the oldest and best preparations is the Luasmin capsule (Brewer). For some patients the Luasmin suppository consisting of theophylline sodium acetate (0.5 Gm.), ephedrine sulfate (60 mg.) and phenobarbital sodium (50 mg.) produces better results than the usual type of suppository which contains only theophylline ethylenediamine.

The various combinations and mixtures of these 3 drugs provide marked relief in a large number of typically allergic asthmatic patients if used, not symptomatically (*i.e.*, when an attack occurs) but prophylactically (*i.e.*, around the clock). Ephedrine is prescribed on arising and at 2 P.M., independently of the presence or absence of symptoms. If bronchospasm should be present and not be relieved by one dose, a second can be taken in forty minutes, and a third in another forty minutes. The routine combination capsule can be taken and followed in thirty minutes by the same ingredients prescribed in liquid form with an antitussive vehicle for faster absorption and relief of both cough and wheeze. If ephedrine does not disturb sleep, it can also be taken on retiring. Whenever it causes insomnia, a mixture of diphenhydramine (37.5 mg.), rac-

ephedrine (150 mg.) and aminophylline (25 mg.) in tablet form (Hyadrine, Searle) is taken at bedtime.

After one week of this regimen, there are usually fewer, if any, attacks. Symptoms become milder and more easily amenable to other treatment.

The amount of air expired in three seconds is usually increased. The total vital capacity often approximates the predicated normal, except in patients in whom there has been some irreversible emphysematous damage to the lung.

Steroid hormones. If the patient is less dyspneic and feels better, but the total vital capacity has not increased to approximately normal levels, a decision must be made as to whether the deviation from the predicated normal is due to spasm not affected by the drugs prescribed, or to fluid retention or inflammation. Adrenocortical steroid hormones can then be used, not therapeutically, but diagnostically.

The adrenal steroid hormones have been a large factor in the change in our concepts of the treatment of all types of bronchial asthma. They have enabled us to discover that degree of recovery beyond which, in the present state of medical knowledge, the patients cannot go. By the use of these drugs we can measure not only the amount of spasm and edema, but also how much irreversible damage the lungs have suffered. Because these agents are given to patients for whom iodides and antispasmodic agents are concomitantly prescribed, the doses can be small. Such patients rarely if ever become dependent upon steroid hormones.

Those in whom there is a history of diabetes, tuberculosis, peptic ulcer, osteoporosis, psychotic episodes or present infection are usually excluded from any such diagnostic procedures. In our series of over 850 patients, only tuberculosis and active infection were regarded as contraindications. In exceptional instances, despite the presence of either tuberculosis or active infection or both, steroid hormones were prescribed along with other therapeutic agents.

One of our diabetic patients fell and broke an arm. The roentgenograms proved the presence of osteoporosis. There was, however, a history of similar mishaps antedating the treatment with steroid hormones. In another patient who took steroid hormones for six months without supervision, active tuberculosis developed, although x-ray studies carried out at the initiation of treatment had not revealed any acid-fast infection. Otherwise, over a period of eight years, no patient in our series suffered any measurable ill effects from either continuous or interrupted treatment.

For the ambulatory patient who, despite iodides and antispasmodic medication, continues to suffer several asthmatic attacks daily, we follow a standard procedure. The patient takes a Luasmin (Brewer) capsule on arising and at 2 P.M., and a Hyadrine (Searle) tablet at bedtime. A liquid ephedrine-iodide-phenobarbital mixture may be prescribed to be taken when necessary for such attacks as may occur. If there is a cough, the antispasmodic ingredients are doubled in strength and either Mercodol, Consol or Cothera (Merrell) is added, so that the teaspoonful-doses contain the standard posologic amounts of both antitussive and antispasmodic medications.

For an average adult weighing 150 pounds, tablets of the various adreno-

cortical steroid hormones are accepted as equivalent in effect, since the doses of the standard tablets are always adjusted on this basis. For the first day, 2 tablets are ingested every four hours so that the total is 8 to 10 tablets. The patient is usually better subjectively before objective improvement occurs. For the second day the dosage can often be reduced to one tablet every four hours. As improvement continues, the interval is changed to five hours for the third day and to six hours for the fourth. On the fifth day the dosage is 3 tablets—one on arising, one at 2 P.M., and another on retiring. The Luasmin capsules and the Hyadrine tablets are continued.

After a week of taking 3 tablets of adrenocortical steroids daily, the tapering-off process begins. On alternate days the patient takes 3 tablets and 2 tablets; when 2 are taken, one is ingested on arising and another twelve hours later. After a week, if progress is satisfactory, the dosage is reduced to 2 tablets daily, and the patient's progress is followed with the vitalometer. For the following week, the dosage is 2 tablets and 1½ tablets on alternate days, taken in fractions on arising, at 3 P.M. and on retiring.

If the patient continues to do well, he may follow his new schedule for a full week before reducing the dose to half a tablet on arising and on retiring. If this schedule proves satisfactory, the dosage is again decreased to half a tablet taken on arising. After a week or two at this dosage level, steroid hormone therapy is stopped. Then ACTH-gel is injected in amounts of 80-160 units every other day for three injections, as a precautionary measure to stimulate autogenous adrenal steroid production, although there is little proof that it does so.

Some patients can be kept at full vital capacity with a daily dose of half or one tablet of adrenal steroid hormones. When given with supplementary medication, this has resulted in no ill effects, to our knowledge. However, the great majority of the patients can be kept under control with supplementary medication alone for weeks, months and years before they need a second course of treatment with steroid agents.

During such periods of medical treatment the precautions for dust diminution are followed, pets are eliminated, bedding is protected, and injection treatment (usually a single annual repository) is given for such allergens as cannot be eliminated. A second course of adrenal steroid hormone therapy may be needed during the peak of the respective pollen seasons for pollen-sensitive patients in whom immunization has not reached satisfactory protective levels.

Should any infection supervene within six months after cessation of treatment with adrenal steroid agents, they are re-administered in a dosage of one tablet or more three times daily, along with antibiotic agents as necessary. Adrenal atrophy may, to some degree, have persisted and the normal steroid output may not be sufficient to combat the stress induced by infection.

All of the patients in our series (more than 850) undergo weight, blood pressure, urine and vital capacity studies—at first each week for four visits, then every two weeks for two visits, then every three weeks for three visits, and then every month or two. Those who need a dosage of half to one tablet daily return every three months for re-evaluation studies.

We permit the patient to keep a supply of the steroid agents on hand, to be taken should bronchospasm recur, provided he assures us that with the first dose he will call his personal physician. The patient's vulnerability to any stress is always explained to him. Only the patient's own doctor can tell him whether the recurrence is due to exposure or to concurrent infection. The physician prescribes the needed supplementary medication. The assurance that medicine is available for weekends, holidays, periods of bad weather, and pending delay until a physician arrives, lessens the patient's anxiety. However, should a patient resume steroid therapy, no matter how intelligently, but without supervision, no further supplies are prescribed.

Miscellaneous

Nebulization is not used except for the treatment of intractable asthma. Although it provides quick transient relief, the vitalometer proves that such symptomatic treatment is not suitable for continued use. Experience has shown that patients who possess nebulizers use them more and more, with less and less effect. When an intelligent patient possesses a nebulizer and finds it effective for occasional quick relief, not more than once or twice in twenty-four hours, there is no reason why he should not continue with it. Epinephrine (1:100) continues to be the most effective drug, and the Burroughs-Wellcome preparation the least expensive commercial product available. Epinephrine in 1:1000 solution will relax bronchospasm in some cases; when it does, this weaker dilution should be prescribed.

Other types of treatment may be used as needed—for example, intermittent positive pressure breathing. All our patients are given some informal psychotherapy. Smoking is not permitted. Almost all asthmatics must be re-educated in proper breathing, and the many who are physically unfit must otherwise be brought into good physical condition.

SUMMARY

Asthmatic patients can be treated successfully for present relief and future freedom from irreversible pulmonary damage, when studied from 4 focal points of view: 1) asthma is considered to be a chronic disorder which may be subclinically present, especially in older patients, 2) the state of the lungs is determined by simple pulmonary function tests, 3) treatment consists of restoring the lungs to full normal function, and 4) drugs are used prophylactically and in sequence to discover the minimum amount of medication which will stimulate satisfactory vital capacity and maximum breathing capacity up to the point of blockage by irreversible change. The drugs prescribed are potassium iodide, ephedrine and the adrenal steroid hormones.

Such drug therapy must be regarded as supplementary to the elimination of environmental allergens and the unavoidable injection therapy for environmental or seasonal allergens. Such combined treatment not only keeps the older patient comfortable, but prevents further irreversible changes and extension to other body systems.

AN EVALUATION OF ORPHENADRINE HYDROCHLORIDE (DISIPAL)

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A cure for "shaking palsy" appears as remote today as one hundred and fifty years ago when Sir James Parkinson first described the syndrome to which his name has become linked. Hyoscine, the belladonna derivatives, the antispasmodics and some of the antihistaminics have been of use, but at best, these agents give only symptomatic relief. They ameliorate rigidity, tremor, general weakness, sialorrhea and oculogyria, relieve mental depression, and postpone the incapacities due to the slow progression of an inexorable disease. Frequently, however, these agents gradually lose their efficacy or cause untoward side-reactions. The surgical approach, although promising in the management of parkinsonism, is still in the developmental stage and is, moreover, a rather heroic procedure justifiable only in selected cases. Therefore, any new drug, even if offering no more than significant symptomatic relief and a satisfactory degree of tolerance with minimal toxicity, deserves serious attention and careful evaluation. Such a drug is orphenadrine hydrochloride (Disipal), the o-methyl analogue of diphenhydramine hydrochloride (Benadryl).

Diphenhydramine, either alone or in conjunction with antispasmodics, has been employed in the management of parkinsonism because of its sedative and soporific effects. Orphenadrine does not share these activities, but is also a mild antihistaminic. It is, in addition, a euphoriant, local anesthetic, and mainly an antimuscarinic agent (1). In the animal it reduces drug-induced tremor, and inhibits canine rigidity-tremor disease (the post-distemper choreiform movements of dogs); it enhances the effect of pentobarbital and is mildly effective as an anticonvulsant against agents such as pentamethylenetetrazol (Metrazol) and nicotine (2).

Doshay and Constable (3) found orphenadrine to be a valuable adjunct in the management of paralysis agitans because it was effective in relieving sialorrhea and oculogyria and appeared to be generally invigorating and free from harmful side-effects.

CLINICAL DATA

During the past eight months we have employed Disipal[1] in conjunction with other specific drugs in the treatment of 125 cases of Parkinson's disease. The treatment periods varied from three weeks to six months and longer. A dosage of 150 mg. daily (50 mg. t.i.d.) was used.Our general impression has been most gratifying, with regard to both its mood-lifting effect and its harmlessness.

[1] Disipal was kindly supplied by Dr. A. Surtshin of the Riker Laboratories, Inc., Los Angeles, California.

However, we too have found that the drug is most effective as an adjuvant and not as the sole medication.

Our group of patients represented each of the 3 etiologic types of Parkinson's disease or paralysis agitans, namely, the postencephalitic, the arteriosclerotic and the idiopathic. Though similar in their general symptomatology, these forms differ in the frequency and severity with which the various signs and symptoms occur. Oculogyric crises and sialorrhea, for instance, are rare in idiopathic and arteriosclerotic paralysis agitans, but common in the postencephalitic variety. This last group is characterized also by marked lethargy, akinesia and speech disorder, whereas rigidity and tremor are usually of moderate intensity, and dysphagia is rarely seen. Rigidity and tremor are predominant and usually most marked in the arteriosclerotic type. The idiopathic form also manifests itself mainly by rigidity and tremor; dysphagia is rare, and akinesia or sialorrhea, if present, is mild. Emotional instability and a tendency toward depression are common to all 3 forms, but respond well to medication regardless of etiology.

We were most impressed by the marked improvement in 21 patients who had previously failed to obtain satisfactory relief from other antiparkinsonism agents. This group was observed most carefully, and is the subject of this report. Twelve of the 21 suffered from postencephalitic parkinsonism, 5 from the idiopathic form, and 4 from the arteriosclerotic form. All were in-patients at our institution and well known to us. Their responses to other antiparkinsonism drugs had already been observed and these observations were useful in the evaluation of the merits of orphenadrine (Disipal). Six of the patients were females, and 15 were males. Their ages ranged from 41 to 77 years, the younger patients being in the postencephalitic group. The average age for the postencephalitic group was 54 years; for the idiopathic group, 56 years; and for the arteriosclerotic group, 66 years. The longest duration of the disease was observed in the postencephalitic group of patients, in whom it ranged between eighteen and thirty-six years, with an average of 25.8 years. The duration of the disease in the idiopathic group ranged from seven to thirty years, with an average of 16.8 years; and in the arteriosclerotic group it ranged from three to eighteen years, with an average of 8.2 years.

During a control period of eight weeks during which the therapeutic regimen remained unaltered, a careful analysis and ratings were made of the severity of the various manifestations of the disease. These included: rigidity, tremor, oculogyria, akinesia, adiadokokinesia, sialorrhea and abnormal mental status. The new medication was then started. One tablet of Disipal (50 mg.) was given three times daily without alteration of the pre-existent medical regimen. Changes in the clinical manifestations were carefully noted and special attention was paid to the detection of any untoward side-effects. Since a subjective element was inherent in the evaluations, whether made by the observer or by the patient, electromyographic examination was employed in an attempt to obtain more objective evidence of a change in rigidity. Four patients in whom rigidity was most marked were selected and examined for this purpose.

RESULTS

The findings are summarized in Table 1. The following conclusions were drawn from our study:

1. The drug was tolerated well, and there were no significant side-effects or serious reactions. Two patients who had unpleasant symptoms ascribable to the drug—difficulty in urination (N.K.) or nausea (E.R.)—nevertheless insisted on continuation of the medication because of other effects that were beneficial.

2. The most striking beneficial effect was the improvement in emotional status with reduction of depression. This improvement was not limited to any specific etiologic group. Twelve of the 16 patients who previously had been depressed became distinctly affable, and 2 others in whom no change of mood could be noted desired further medication because it made them "feel better." In 2 patients with severe depression the drug was ineffective. One patient with an extremely aggressive attitude experienced no change, and 1 other patient with a previously normal mood manifested signs of depression.

The next significant change occurred in the patients who suffered from sialorrhea, most common in the postencephalitic form of parkinsonism. In 10 of the 18 patients with this disturbance, there was mild to marked improvement, particularly in those in whom the sialorrhea had been most marked. Those who showed no change in this respect had had, with 1 exception, only mild sialorrhea (2+ to 1+) during the pretreatment period. Sialorrhea is not primarily produced by parkinsonism, but by the tilt of the head. Thus, the observed reduction in sialorrhea seemed to be due to better control of the muscles of deglutition and to decreased rigidity of the cervical muscles.

4. Nine patients in the postencephalitic group suffered from attacks of oculogyria, and required frequent hypodermic injections of hyoscine. Only 2 of the 9 were completely relieved of this annoying phenomenon. Thus, there would seem to be a limit to the usefulness of the drug in the postencephalitic form of the disease. However, Doshay and Constable (3) reported 100 per cent improvement in oculogyria. They did not state the ages of their patients or the duration of the disease. The average duration of the disease in our postencephalitic patients was 25.8 years. Perhaps this long duration accounts for the failure of our patients to obtain relief.

5. Rigidity is probably the most severe symptom, from the patient's perspective; he feels encased in his own musculature. Rigidity occurs particularly in the arteriosclerotic and idiopathic forms. Of the 21 patients, 11 experienced mild to marked relief of this symptom, and 10 were unaffected. It was our first impression that this relief from a "frozen" state accounted for the elevation in mood, but since patients who obtained no decrease in rigidity also became more affable, it would appear that the drug has inherent euphoriant properties.

6. Least impressive was the effect on tremor. In the experimental animal, Disipal prevents the effects of 1,4-dipyrrolidino-2-butyne (Tremorine); our patients showed no significant changes due to its use.

TABLE 1

TABLE 1

Effect of Disipal Combined with Other Agents in 21 Patients with Parkinson's Disease Who Had Failed to Respond to Other Specific Drugs

Patient		Rigidity		Tremors		Oculogyric Crisis		Akinesia		Adiadoko-kinesia		Salivation		Mental Status		Side-reactions of Disipal	Duration of Disease (yrs.)	No. of Yrs. in Hospital
Name	Sex & Age	Bfr.*	Aft.*	Bfr.	Aft.	Bfr.	Aft.	Bfr.	Aft.	Bfr.	Aft.	Bfr.	Aft.	Bfr.	Aft.			
Post-encephalitic Group																		
S.G.	M 55	4+	1+	2+	2+	1+	1+	2+	2+	1+	1+	4+	1+	D†	E†	None	28	6
M.Z.	M 49	2+	1+	2+	2+	2+	0	3+	1+	2+	2+	2+	2+	D	E	None	24	12
S.W.	M 43	3+	1+	1+	1+	2+	0	1+	1+	1+	1+	2+	2+	MD	E	None	33	3
J.A.	M 58	3+	3+	2+	2+	0	0	2+	2+	2+	2+	2+	2+	AA	AA	None	26	9
T.J.	M 72	3+	1+	4+	4+	0	0	2+	2+	1+	1+	3+	1+	MD	E	None	36	15
E.F.	F 50	2+	2+	2+	2+	0	0	2+	2+	2+	2+	2+	2+	MD	WD	None	24	5
N.K.	M 66	3+	1+	3+	3+	2+	2+	2+	2+	2+	2+	3+	1+	MD	E	None	27	11
S.H.	M 44	2+	2+	2+	2+	2+	2+	2+	2+	Same		3+	1+	D	D	None	26	12
S.A.	M 61	3+	3+	2+	2+	None		2+	2+	Same		3+	2+	MD	E	None	20	10
H.T.	F 41	2+	2+	2+	2+	2+	2+	2+	2+	2+	2+	3+	2+	MD	WD	None	18	14
B.L.	M 53	4+	2+	2+	2+	2+	2+	2+	2+	Same		3+	1+	NM	E	None	22	5
G.M.	F 60	2+	2+	Same		Same		Same		Same		Nil		D	D	None	26	12
Idiopathic Group																		
N.K.	M 56	4+	1+	3+	1+	Nil		2+	2+	3+	3+	2+	1+	D	E	Difficult urination	14	7
G.A.	M 70	3+	3+	3+	3+	Nil		2+	2+	3+	3+	2+	2+	MD	MD	None	7	4
S.L.	M 56	4+	1+	3+	3+	Nil		No change				3+	1+	MD	E	None	8	1
N.E.	F 55	3+	1+	3+	1+	4+	1+	2+	2+	2+	2+	None		NM	E	None	30	5
W.B.	M 57	3+	3+	2+	2+	Nil		2+	2+	2+	2+	None		NM	D	D	25	2
Arteriosclerotic Group																		
I.S.	F 65	4+	2+	1+	1+	Diplopia		2+	2+	2+	2+	1+	1+	MD	MD	None	3	1
L.W.	M 77	4+	1+	3+	1+			2+	2+	1+	1+	2+	1+	MD	E	None	6	2
A.L.	M 64	3+	3+	3+	3+			1+	1+	1+	1+	2+	0	NM	E	None	18	6
E.R.	F 58	3+	3+	3+	3+			2+	2+			3+	0	MD	WD	Nausea	6	1

* Bfr. = Before Disipal. Aft. = After Disipal.

† D = Depressed. N = None. MD = Mildly depressed. AA = Aggressive attitude. WD = Wants Disipal. NM = Normal mood. E = Euphoric.

No objective evaluation could be made of the effect on akinesia and adiadokokinesia. It should be noted, however, that some patients who had been prevented by these disabilities from engaging in occupational therapy and group gymnastics were able to participate during Disipal therapy.

Electromyographic recordings demonstrated graphically the marked improvement in rigidity in 2 of the 4 patients studied. The pre-treatment curves were typical of those found in parkinsonism. In normal resting muscle no electromyographic activity is detected and a horizontal (isoelectric) line is recorded, but the "resting" curve of parkinsonian muscle is characterized by persistent undulations. Likewise, the regular activity waves of normal muscle are replaced in parkinsonism by irregular and chaotic changes. This type of abnormal wave is indicative of the unfulfilled (cogwheel) response of the muscle mass to rest, voluntary contraction, stimulation and relaxation. After six weeks of Disipal therapy, 2 of the 4 patients demonstrated almost normal curves during both the resting and the active phases. In the 2 other patients, the clinically observed decrease in rigidity did not manifest itself in the electromyogram.

In the course of this study, we also treated with Disipal a number of patients with multiple sclerosis in whom rigidity was prominent. The beneficial results were not as marked as in parkinsonism, but in at least some of the patients the rigidity was decreased. Although patients with multiple sclerosis are usually spontaneously euphoric, a depressed mood may be encountered. In such cases, the depression could be relieved with Disipal in a manner similar to that observed in the patients with Parkinson's disease.

SUMMARY

A new drug, orphenadrine hydrochloride (Disipal), has been utilized in a dosage of 50 mg. three times daily in 125 cases of severe parkinsonism, and its action observed in detail in 21 patients who had not responded to previous specific drug therapy. Disipal was always used in combination with other agents and never as the sole remedy. It was most effective in relieving rigidity and in overcoming the depression usually present in parkinsonism. Its antisialorrheic effects were noteworthy. It was ineffective in the prevention of oculogyric crises, and in the relief of tremor.

Orphenadrine is an important drug in the treatment of parkinsonism. Release from rigidity and an elevation of mood are highly desirable effects in this malicious disease.

Addendum

Since submitting this manuscript, we have used another form of orphenadrine, namely, orphenadrine citrate. This preparation in a dosage of 100 mg. twice daily has proved to be highly effective, producing even greater release of muscular rigidity.

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LEYDIG-CELL HYPERPLASIA IN ELDERLY MEN

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Carcinoma of the prostate gland is said to result from a disturbance of the ratio and quantity of androgens and estrogens in older men. Since the interstitial cells (Leydig cells) of the testis secrete androgens, one might expect hyperplasia in all cases of prostatic cancer. However, most studies (1) have indicated there is no significant alteration of the interstitial-cell content of the testis in patients with prostatic carcinoma.

In 1943 Warren and Olshausen (2) found a paucity of cases of Leydig-cell hyperplasia in the literature, and added 2 cases to the 10 previously reported. In contrast, Blundon, Russi and Bunts (3) stated that "interstitial cell hyperplasia is an apparently normal finding in the testis of senility." Furthermore, they thought that no definite line of demarcation separates neoplasia from hyperplasia in cases of massive interstitial-cell proliferation, implying that half of the 50 cases of interstitial-cell tumor reported in the literature may actually have been hyperplasia.

Since there is some confusion concerning the frequency of occurrence of Leydig-cell hyperplasia, its significance, and its differentiation from interstitial-cell tumor, this study was undertaken.

MATERIAL

Thirty-two patients with carcinoma of the prostate gland were treated by orchiectomy and administration of estrogen.

Their average age was 69 years, with a range from 59 to 82 years. Routine hematoxylin-and-eosin stained sections from their testes were studied, and the findings were correlated with the clinical aspects in each case.

RESULTS

As shown in Table 1, the number and distribution of interstitial cells were considered normal in 18 of the 32 patients, diminished in 8, increased in 4, and indicative of hyperplasia in 2 (6.2 per cent). This in accord with the 7.3 per cent incidence of hyperplasia reported by Warren and Olshausen (2) in a review of 370 testes.

Thirteen of the 32 patients had received stilbestrol prior to orchiectomy. In 8 of these the number of Leydig cells was diminished, and in 5 it was normal. Neither of the 2 patients with hyperplasia had received estrogens. This is of interest, because Bonser and Hawksley (4) reported a series of benign and malignant interstitial-cell tumors produced in mice by the injection of estrogens. In man, estrogen appears to produce just the opposite effect, that is, a decrease in the number of interstitial cells.

The average age of the men in this series was 69 years. Decreased spermatogenesis and atrophy of the seminiferous tubules were found in 30 of the 32 cases. Since only 13 of these patients received stilbestrol prior to castration,

TABLE 1
Distribution of Testicular Cells in 32 Men with Prostatic Carcinoma

Type of Cell	Cell Count			
	Normal	Increased	Decreased	Hyperplastic
Interstitial cells	18	4	8	2
Spermatocytes	2	0	30	0
Stromal fibroblasts	18	14	0	0
Sertoli cells	26	0	6	0

FIG. 1. Interstitial-cell hyperplasia resembling interstitial-cell tumor, except for the presence of 1 small seminiferous tubule in the lower left field. Demarcation from the seminiferous tubule in the lower left field. Demarcation from the seminiferous tubules on the right is sharp. Magnification 100×.

this tubular atrophy was probably related to the age of the patient rather than to the administration of estrogens.

The stroma between the seminiferous tubules was fibrotic in 14 patients, only 7 of whom had received stilbestrol. Therefore, fibrosis also was probably related more to the aging process than to the effects of stilbestrol.

The number of Sertoli cells appeared to be normal in 26 cases, and decreased in 6 cases in which marked tubular atrophy was also present. Huggins (5), Lewis and Stockard (6), and others believe that Sertoli cells secrete estrogens, as they have found Sertoli-cell tumors in feminized male dogs.

However, feminizing changes such as gynecomastia have also been found in men with Leydig-cell tumors. The question of whether Sertoli cells secrete or store estrogens is not yet settled.

Hyperplasia

Neither of the 2 patients with Leydig-cell hyperplasia had received estrogens prior to castration. Spermatogenesis was still evident in the testes of one of them, aged 70, and was diminished in the testes of the other, aged 67. Tubular atrophy has been said to produce an apparent or relative hyperplasia of the interstitial cells. The Leydig-cell hyperplasia was bilateral in each patient and there was no suggestion of a testicular tumor. Figure 1 is a photomicrograph of a histologic section from one of these testes. It shows massive interstitial-cell hyperplasia, which is demarcated from the seminiferous tubules and resembles a Leydig-cell tumor except for the small seminiferous tubules in the lower left field. Differentiation between tumor and hyperplasia is established on the basis of the criteria that tumors are often encapsulated or demarcated from the host tissue, and that the seminiferous tubules are supposed to be replaced rather than surrounded by tumor cells.

DISCUSSION

The interstitial cells of the testes are either of epithelial or connective-tissue origin, this being an unsettled question among various authorities. They usually are in groups of 4 or 5 cells, lying between the seminiferous tubules. They normally are numerous in fetal life, probably due to stimulation from the maternal anterior pituitary-like hormones. At birth a pronounced reduction occurs, but at puberty they increase again. Between the ages of 10 and 19 they are most numerous, decreasing during adult life. With senility or any condition that produces atrophy of the seminiferous tubules, there is a relative increase in the number of interstitial cells. Since androgens are secreted by these cells, one might expect hyperplasia to be commonly associated with carcinoma of the prostate gland. However, such is not the case. Even with interstitial-cell tumors, which may produce premature puberty in children, in adults there usually is no evidence of increased androgen secretion except for increased excretion of urinary 17-ketosteroids.

In differentiating Leydig-cell tum fromor hyperplasia, the finding of seminiferous tubules within the cell mass should be indicative of hyperplasia. However, Christeson and Nettleship (7) contend that interstitial cells are epithelial in origin, arising from seminiferous tubules. Therefore, they believe that the presence of tubules within the mass is compatible with the diagnosis of Leydig-cell tumor. Their patient had a large palpable tumor, which is not usually found with hyperplasia. Most patients with interstitial-cell tumors are

under 50 years of age, whereas hyperplasia usually occurs in men over 50 years of age and tends to be bilateral. Tumors are usually encapsulated, in contradistinction to hyperplasia.

Since only 6 of our 32 patients had an increased number of testicular interstitial cells and only 2 had hyperplasia, there was no histologic correlation between the number of interstitial cells and the occurrence of prostatic carcinoma. Although estrogens may produce interstitial-cell tumors in mice, in human subjects the administration of estrogens does not predispose to either interstitial-cell hyperplasia or tumor formation. Indeed, estrogens appear to induce a decrease in the number of interstitial cells as well as atrophy of the seminiferous tubules.

SUMMARY

The testicular findings in 32 patients (average age, 69 years) with prostatic carcinoma have been correlated with the clinical course, and also with preorchiectomy estrogen therapy in 13 cases.

Instead of the expected increase in the number of interstitial (Leydig) cells in these 32 elderly men, there was a normal or a decreased number in 26. Leydig-cell hyperplasia was found in only 2 patients, an incidence of about 6 per cent. A decrease in the number of interstitial cells, as well as tubular atrophy, was associated with estrogen therapy prior to orchiectomy. Thus, the administration of estrogens apparently does not predispose to interstitial-cell hyperplasia.

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Abstracts of Current Literature

Carcinoma of the Pancreas Associated with Chronic Relapsing Pancreatitis.

Bartholomew, L. G.; Gross, J. B., and Comfort, M. W. *Gastroenterology* **35:** 473 (Nov.) 1958.

Two case reports are given of carcinoma of the pancreas apparently of ductal origin, that developed in patients with long-standing chronic relapsing pancreatitis. The first manifestations of the disease were recurrent attacks of severe abdominal pain. As they continued, each patient experienced steatorrhea, diabetes mellitus, pancreatic calcification, and jaundice. After fourteen and twenty-one years, respectively, the severity of pain and the sequelae of pancreatic insufficiency resulted in another surgical attempt to relieve these symptoms. Carcinoma was found at laparotomy in the first patient, and at necropsy in the second. The coexistence of chronic pancreatitis and of pancreatic carcinoma apparently is infrequent inasmuch as few cases have been reported. Because of the carcinogenic effect of chronic inflammation and irritation, the occurrence of carcinoma in cases of long-standing inflammation of the pancreas would not be surprising. However, no definite relationship between the two has as yet been established. Since the preparation of this paper, 2 additional cases of carcinoma of the pancreas associated with chronic relapsing pancreatitis have been observed and the occurrence of still another come to the authors' attention.

Calcification of the Coronary Arteries.

Blankenhorn, D. H. 31st Sci. Session, Am. Heart Assoc., October, 1958; Abstract, *Circulation* **18:** 695 (Oct.) 1958, Part 2.

At present, the clinical diagnosis of coronary atherosclerosis depends upon recognition of some manifestation of impaired myocardial blood supply. More direct diagnostic technics yielding information as to the size, character and location of coronary lesions are needed. Coronary arteriography can provide such information, but entails sufficient hazard and labor that it does not appear applicable to routine use. Calcification in the coronary arteries can be visualized by x-ray. This technic, previously proposed by others, entails no risk and can be made routine. A study was performed to determine what calcific lesions occur in human coronary arteries and what might be learned if these calcifications were recognized during life. Postmortem x-ray examination of 80 hearts from unselected patients 17 to 95 years of age indicated that: coronary calcification can be differentiated from other intracardiac calcification by location and appearance; coronary calcification occurs only in atheromatous lesions; a calcific plaque 5 mm. or more long occurs in 40 per cent of hearts (32 of 80). Present day x-ray technic allows consistent recognition of solitary lung nodules which exceed 3 mm. If improved x-ray technic could effect comparable recognition of coronary calcification, exact information regarding coronary atherosclerosis would become available to the clinician in up to 40 per cent of adults.

Cancer of the Stomach after Gastric Resection for Peptic Ulcer.

Côté, R.; Dockerty, M. B., and Cain, J. C. *Surg., Gynec. & Obst.* **107:** 200 (Aug.) 1958.

A study was made of 17 cases of gastric cancer which occurred over a 50-year period in patients in whom gastric resection (5 patients) or gastroenterostomy (12 patients) had been performed sometime previously for peptic ulcer. The lesions included 1 sarcoma, 1 heman-

gioendothelioma, and 15 adenocarcinomas. The adenocarcinomas usually occurred at the line of anastomosis in the patients who had undergone resection, and in the lower part of the stomach in the others. The clinical findings in instances of both benign and malignant lesions were not unusual, except that 3 patients had achlorhydria following a test meal. None of the resected stomachs showed hypertrophy of the gastric mucosa or precancerous lesions, but there was thinning and smoothing of the mucosa in at least one area in each. The symptoms of cancer were those usually seen, but the diagnosis was difficult to make because of the history and the previous operation. The lesion was not demonstrated roentgenographically in most of the cases that had undergone gastric resection. The evidence of gastritis did not bear a relationship to the development of carcinoma. The prognosis for patients with gastric cancer following peptic ulcer is poor, but 4 patients in this series have had a prolonged survival. This study indicates that carcinoma of the stomach rarely develops in patients who have been treated for peptic ulcer by gastric resection or by excision of the ulcer.

Coronary Visualization by Occlusion Aortography During Induced Cardiac Arrest in the Intact Subject.

Dotter, C. T., and Frische, L. H. 31st Sci. Session, Am. Heart Assoc., October, 1958; Abstract, *Circulation* **18:** 713 (Oct.) 1958, Part 2.

Attempts to visualize man's coronary arteries by thoracic aortography have been literally and figuratively washed out by aortic blood flow. Even alarmingly large doses of concentrated contrast media, used in a brute-force effort to compensate for dilution, are largely swept out of the aorta to cause undesired systemic effects rather than coronary visualization. These effects of blood flow are eliminated by injecting the contrast agent during a brief period of induced cardiac arrest in combination with total occlusion of the ascending aorta. Over 1,000 experimental studies in dogs and recent application to man reveal the approach to be safe, simple, reliable, and highly effective. The technic of examination is as follows: A double-lumen balloon catheter, introduced through a suitable peripheral artery, is maneuvered under fluoroscopy until its tip lies about an inch above the level of the aortic valves. A small dose of acetylcholine is injected through the catheter, almost instantly producing cardiac arrest; whereupon the balloon is rapidly inflated, contrast agent injected, and serial films made. The arrest is self limited; reversion to normal sinus rhythm occurs within about eight to fifteen seconds. The risk of the procedure is judged to be minimal, and improvement in radiographic detail is striking. Intercoronary anastomoses are routinely demonstrated in normal dogs, as are major and minor abnormalities in the coronary arteries of man.

Jaundice Occurring in a Patient Treated with Chlorothiazide.

Drerup, A. L.; Alexander, W. A.; Lumb, G. D.; Cummins, A. J., and Clark, G. M. *New England J. Med.* **259:** 534 (Sept. 11) 1958.

The occurrence of intrahepatic obstruction jaundice in a patient receiving chlorothiazide is reported. A 62-year-old woman with a long history of diabetes and chronic congestive heart failure, in the six-month period prior to this episode, had received no medication other than insulin, digitalis and mercaptomerin. After a poor response to this treatment, 500 mg. of chlorothiazide was given daily in addition to digitalis and NPH insulin. Itching of the skin commenced within four days and jaundice appeared four weeks after this medication was started. The diagnosis was made following the demonstration of abnormalities in liver function, needle biopsy of the liver, and exploratory laparotomy. Following operation, the patient had an uneventful convalescence. Results of liver function studies returned to normal within two months. At the time of death from congestive heart failure nine months later, necropsy showed no evidence of obstruction of the biliary passages, only minimal fibrosis, no periportal inflammation, and healing of necrotic areas. The abnormalities that had been observed in this patient were thought to be due to chlorothiazide.

Massive Venous Occlusion: its Pathogenesis and Management.

Edwards, W. S. *South. M. J.* **51:** 1056 (Aug.) 1958.

Since the pathogensis of massive venous occlusion of the legs is not clear, there has been no uniform approach to treatment. Recent studies indicate that the occlusion results from iliac and femoral thrombosis of undetermined origin. Since the venous pressure drops after sympathetic blockade, venous spasm seems to be second in importance as a causative factor. This also indicates that arterial spasm, if present, is not a dynamic factor. If it is present, it may be a protective mechanism to prevent further pooling of blood in the extremity. Thrombectomy with removal of as much clot as possible approaches the ideal treatment more nearly than any other used thus far. Spinal anesthesia, as an effective sympathetic nerve block, has lowered venous pressure in each instance when it has been used as the original method of treatment. Heparin is useful as an adjunct to therapy to prevent recurrence of thrombosis or occlusion of important collateral vessels. Therefore, present treatment would consist of spinal anesthesia, high elevation of the leg without manipulation (which has proved harmful because of the development of pulmonary emboli), intramuscular or intravenous administration of heparin for ten to fourteen days, and immediate thrombectomy if the symptoms of arterial insufficiency are not quickly relieved by these conservative measures.

The Action of Glucagon-Insulin Mixtures in Diabetic Patients.

Elrick, H.; Arai, Y., and Hlad, C. J., Jr. *J. Clin. Endocrinol. & Metab.* **18:** 825 (Aug.) 1958.

The effects of glucagon-insulin mixtures were tested in 30 unselected hospitalized diabetic patients. The combination increased glucose utilization in the forearm more than did insulin alone. The response appeared to be partially dependent upon the fasting blood sugar level but not upon the severity of the diabetes. It also was influenced by the ratio of glucagon to insulin in the infusion. Neutralization of the opposing effect of the two hormones on arterial glucose levels (stabilization) was seen when the fasting arterial glucose concentration was above 170 mg./100 ml. if the ratio of glucagon to insulin was 0.26 to 0.90. However, if the arterial glucose level was below 170 mg./100 ml., or the glucagon-insulin ratio above 90, the hyperglycemic effect of glucagon persisted. These findings support the hypotheses that glucagon and insulin in combination may offer a way to maintain the constancy of blood glucose and liver glycogen levels despite increased peripheral utilization of glucose. It is also possible that glucagon, because it is effective in stabilizing blood sugar concentration and increasing peripheral glucose uptake when the blood sugar level is above 170 mg./100 ml., may prove useful in the treatment of impending or actual diabetic acidosis. It already has been shown to relieve insulin reactions because it counteracts the hypoglycemic action of insulin. It appears that it will become useful in the management of derangements in diabetic control, whether they be hyperglycemic or hypoglycemic in nature.

Spontaneous Regression of Cancer.

Everson, T. C. *Connecticut Med.* **22:** 637 (Sept.) 1958.

Among more than 1,000 cases of spontaneous regression of cancer reported in the world literature or through personal communcations, 90 have had enough documentation, including histologic confirmation of the malignancy, to justify acceptance as true examples of spontaneous regression of carcinoma. Spontaneous regression occurred in order of frequency in cases as follows: neuroblastoma, 19; malignant melanoma, 11; chorio-epithelioma, 9; bladder, 9; breast, 8; soft-tissue sarcoma, 5; uterus, 4; stomach, 4; colon and rectum, 3; hypernephroma, 3; oral cavity, 3; osteogenic sarcoma, 3; metastatic carcinoma, primary, unknown, 2; ovary, 2; and liver, larynx, lung, pancreas and thyroid, 1 each. Illustrative cases are reviewed. Regression of presumptive metastases diagnosed only by roentgenograms and not included in the 90 cases were most frequently noted in chorio-epithelioma,

malignant melanoma, osteogenic sarcoma, and hypernephroma. When prolonged arrest of the growth of cancer was noted in these studies, it was most commonly found to occur in carcinoma of the breast, carcinoma of the thyroid, and carcinoma of the prostate. Endocrine influences, unusual sensitivity to inadequate radiation or other therapy, fever or acute infection or both, allergic or immune reactions, interference with the nutrition of the cancer, removal of the carcinogenic agent, complete surgical removal of the cancer, and incorrect histologic diagnosis of malignancy are each taken into consideration as possible factors in the spontaneous regression of cancer. Spontaneous regression of cancer 1) supports the concept of the biologic control of cancer, 2) emphasizes the need for caution in interpreting the results of chemotherapy, 3) points to the need to consider spontaneous regression in the evaluation of prognosis of certain cancers, and 4) may be of some psychotherapeutic value to the patient with a carcinoma that is not amenable to surgical or radiation treatment.

Anabolic Steroids in Treatment of Uraemia.

Gjørup, S., and Thaysen, J. H. *Lancet* **2:** 886 (Oct. 25) 1958.

Nilevar (norethandrolone) orally in dosages of 50 to 100 mg. daily, and Durabolin (nondrolone) intramuscularly in dosages of 50 mg. per week, were tested in 10 cases of severe chronic renal failure. Increased appetite, retention of lean tissue, gain in body weight, and improvement in the clinical condition occurred in all. There was no increase in biochemical uremia. The most common immediate reaction to therapy was a decrease in the levels of blood urea nitrogen and NPN. Only minimal virilizing effects were noted in some patients. Nilevar caused severe and prolonged withdrawal bleeding in 1 patient. These steroids appear to break the vicious circle of progressive uremic intoxication and approaching cachexia in patients with severe chronic renal failure. The improvement they produce may enhance the chance for adequate surgical or medical therapy. The ultimate prognosis depends upon the possibilities for improving the underlying renal disorder. These steroids have also been tested in acute renal failure but their use therein should be restricted to centers where supplementary hemodialysis can be carried out if necessary.

Acute Myocardial Ischaemia: Significance of Plasma Transaminase Activity.

Goble, A. J., and O'Brien, E. N. *Lancet* **2:** 873 (Oct. 25) 1958.

Plasma glutamic oxalacetic transaminase levels, estimated daily, are a sensitive index of timing and probable degree of myocardial necrosis. They provide a new method for the study of myocardial ischemia. In a study of 18 patients with severe episodes of cardiac pain, not associated with clinical or electrocardiographic evidence of recent myocardial infarction and not relieved by rest or nitrites, serial estimations of plasma glutamic oxalacetic transaminase (PGOT) activity were made for at least seven days. For comparison, similar estimations were made for periods of five to twenty days in 25 normal subjects and 20 patients with a history of angina pectoris or previous myocardial infarction. Among these latter groups, the individual maximum range of serial PGOT levels was 10 units. Rises of more than 15 units were, therefore, considered abnormal, and rises of 10 to 15 units probably abnormal. Among the 18 patients with long-continued cardiac pain, 12 had small increases in PGOT levels, and 11 of them had a subsequent rise in sedimentation rate, indicating myocardial necrosis. The patterns of PGOT indicated single episodes of necrosis in some patients with isolated attacks of pain, and repeated episodes in those with attacks of recurrent pain. Six patients had no evidence of muscle necrosis following their attacks of pain. This was interpreted to mean that prolonged severe pain, even with such phenomena as dyspnea, sweating and fall in blood pressure, does not denote significant myocardial necrosis but suggests prolonged myocardial ischemia, during or following which myocardial necrosis may occur. The necrosis may even be delayed for days or weeks, during which time the patient may notice a vague heaviness in the chest or minor attacks of pain that are relieved by nitrites. Changes in the electrocardiogram consisting of depression of S-T segments and

inversion of the T waves were present in 8 patients, but in 2 of these there was no evidence of myocardial necrosis. This suggests that such changes are produced by a considerable degree of myocardial ischemia rather than by the necrosis that commonly ensues. Another phase of the study of the electrocardiogram showed that, in patients with a previous infarction, extensive myocardial necrosis may occur before any new change appears in the electrocardiographic pattern. Further study of this method is indicated in an attempt to clear the confusion in terms used to describe the syndromes of cardiac pain not associated with myocardial infarction. Any new terminology must recognize that cardiac pain indicates myocardial ischemia, that rises in sedimentation rate and PGOT levels indicate mycardial necrosis, that alterations in the electrocardiogram indicate the localization of the myocardial ischemia or necrosis, and that repeated small episodes of myocardial necrosis may summate to produce the electrocardiographic pattern of transmural myocardial infarction.

THE EFFECT OF ESTROGEN, ANDROGEN, AND THYROID IN DEGENERATIVE JOINT DISEASE.

Hellbaum, A. A.; Ishmael, W. K.; Duffy, M. L., and Payne, R. W. *J. Gerontol.* **13:** 163 (April) 1958.

This report presents the response to anabolic hormones of 431 patients with degenerative disease of the joints. Cases of hyperthyroidism, hypertension and cardiac disease were excluded from the study. Approximately one-third of the patients were studied by a double-blind technic, using a placebo and combinations of estrogen and androgen with and without the addition of thyroid in the form of thyroid globulin (Proloid). The results of this study were similar to those obtained with known preparations. In both, the addition of thyroid enhanced the benefit obtained. Proloid alone in a 16-mg. dosage benefited only a small proportion of the patients so treated. The combined results of the two studies showed that in 68 per cent of 182 patients who received an estrogen-androgen combination there was some improvement, response being evaluated by means of subjective factors such as pain, stiffness, fatiguability, appetite, sleep pattern, spontaneity, alteration in strength, work activity and work capacity. The proportion benefited among 143 patients who received estrogen-androgen with Proloid was 81.3 per cent. Untoward reactions were limited to uterine bleeding in 3 elderly women and the occurrence of acne in 2 other women. Since the original study, the incidence of uterine bleeding has been reduced almost to nil by reducing the dosage of ethinyl estradiol in the combination from 0.01 to 0.005 mg., while the 2.5-mg. dosage of methyltestosterone and the 16-mg. dosage of Proloid remained the same.

ZUM PROBLEM DER PHYSIOSCLEROSE. UNTERSUCHUNGSERGEBNISSE CHEMISCHER ANALYSEN DER VENA FEMORALIS BEI DIABETIKERN. (THE PROBLEM OF PHYSIOSCLEROSIS. RESULTS OF CHEMICAL ANALYSES OF THE FEMORAL VEIN IN DIABETIC PATIENTS).

Hevelke, G. *Ztschr. f. Alternsforsch.* **12:** 217 (Dec.) 1958.

The femoral veins of 32 diabetic patients aged 50 to 80 were analyzed chemically as to dry and ash residue and as to calcium, total cholesterol and nitrogen content. The values obtained were compared with those obtained in previous studies of chemical changes due to aging in the femoral veins of persons of the same age but free of metabolic disease. The dry residue and nitrogen content showed no unequivocal differences between the two groups, but the calcium and total cholesterol contents in the venous walls of the diabetic patients were increased in comparison with the values in nondiabetic patients, especially in the highest age groups. Most striking was the high-grade concentration of cholesterol in the femoral veins of diabetic patients. These studies show that the veins of the large extremities in diabetes do not escape involvement. (From author's summary.)

THE USE OF A STEROIDAL SPIROLACTONE IN THE TREATMENT OF ASCITES IN HEPATIC CIRRHOSIS.

Kerr, D. N. S.; Read, A. E.; Haslam, R. M., and Sherlock, S. *Lancet* **2:** 1084 (Nov. 22) 1958.

A steroidal spirolactone, Sc8109, known to antagonize aldosterone in laboratory animals, was administered to 3 patients with cirrhosis and intractable ascites. A sodium and water diuresis occurred in 2 patients but the third did not respond. Intramuscular injection of the microcrystalline preparation resulted in slow absorption of the drug, the maximum effect being obtained about a week after starting treatment. Some drug action was detectable two weeks after administration. Pain at the injection site was common but no other toxic effects were noted. These brief clinical trials suggest that the drug will be useful in controlling ascites resistant to standard treatment. (Authors' summary) The addendum to this paper states that 1 additional patient who received microcrystalline medication intramuscularly showed an increased urinary sodium output but no loss of ascites. A preparation in sesame oil, thought to be better absorbed, was given to 2 patients. In both, the sodium diuresis was associated with weight loss and clinical relief of edema and ascites. The unresponsive patient (reported above) received one injection of the preparation in oil without a significant increase in urinary sodium or volume. This suggests that poor absorption was not the primary factor in her failure to respond to the microcrystalline preparation.

NEUE EXPERIMENTELLE BEITRÄGE ZUR TUBERKULOSTATISCHEN WIRKUNG UND ZUR TOXIZITÄT VON VIOMYCIN. (NEW EXPERIMENTAL CONTRIBUTIONS ON THE TUBERCULOSTATIC ACTION AND TOXICITY OF VIOMYCIN).

Kradolfer, F.; Neipp, L., and Tripod, J. In: Neue Tuberkulostatika und Tuberkulostatika-Resistenz von Tuberkelbacterien. Symposium at University Medical Clinic, Freiburg, February 10 and 11, 1958. Ed: A. M. Walter; (Tuberkulosearzt Monogr. "Tuberkulose-Bücherei"), Stuttgart 1958, p. 57; through Ciba Literature Review **3:** 338, 1958.

Vionactane is a viomycin salt in which 2 molecules of viomycin base are combined with 1 molecule of sulfuric acid and 2 molecules of pantothenic acid. This antibiotic is used primarily in the treatment of tuberculosis. Bacteriologic tests suggest that Vionactane is also suitable for use in infections caused by other pathogens. It does not have the drawbacks attendant upon the broad-spectrum antibiotics, for it also inhibits the growth of fungi and staphylococci. The tuberculostatic effect of viomycin pantothenate is at least equal to that of viomycin sulfate in vivo. The pantothenate, however, proves to be considerably better tolerated. Following oral administration, Vionactane is excreted in the urine in such an effective form and concentration that its use is indicated in renal tuberculosis, possibly even despite a certain nephrotoxic effect. The antibacterial mechanism of action of Vionactane is still largely unknown, but it differs from that of streptomycin and other tuberculostatic agents (isonicotinic acid hydrazide, p-amino-salicylic acid) in that no cross-resistance develops. Moreover, coliform bacilli do not behave towards viomycin in the same way as they do towards streptomycin. As in vitro tests have shown, different morphologic changes occur.

NEURO-PSYCHIATRIC OBSERVATIONS IN AN OLD PEOPLE'S HOME. STUDIES OF MEMORY DYSFUNCTION IN SENESCENCE.

Kral, V. A. *J. Gerontol.* **13:** 169 (Apri.) 1958.

The residents of an Old People's Home, 71 men and 91 women, with a mean age of 79.4 years, were investigated psychiatrically and neurologically. Roughly two-thirds of the population showed deficient memory function on clinical examination and the usual memory

tests. Two types of memory dysfunction could be distinguished: impaired recall of specific remote memories and progressive impairment of recent memory with its psychologic consequences, leading to a senile amnestic syndrome. Both types of memory impairment were significantly related to advancing age. The amnestic syndrome was significantly more frequent in women than in men. There was no significant relationship between memory dysfunction of either type and the presence or absence of functional psychotic signs, cerebrovascular disease, degenerative extrapyramidal disease, hypertension, or diabetes, although some of these diseases were positively related to advancing age. (Author's summary.)

Reperti Epatobiotici nella Senescenza. (Liver Biopsy Findings in Old Age).

Leonardi, P. *Gior. Gerontol.* **5:** 139, 1957; Excerpta Med. (Gerontol. & Geriatrics) **1:** 77 (Aug.) 1958.

A study was made of the histologic and histochemical aspects of fragments of liver obtained by biopsy from 49 persons aged 60 to 79 years. In the cases without signs of hepatopathy (16) some of the known characteristics of the senile liver were oberved (liver cells rich in pigment, slight sclerotic lesions of the parenchyma, congestion of the suprahepatic veins, slight vascular alterations of arteriosclerotic type). The histochemical reactions for glycogen, ribonucleic acids, phosphatases, and iron were normal. The regenerative capacity of the liver cells, judged on the basis of the dimensions of the nuclei and of the nucleoli, was also practically normal. In the cases with hepatopathy (12 cases of sclerosis, 7 of hepatic sclerosis, 6 of hepatic neoplasia, 3 of marked steatosis, 1 each of acute hepatic atrophy and of acute hepatitis), it could not be shown that the senility had a particular influence on the histologic and histochemical patterns characteristic for the respective diseases. It is asserted, also with reference to 2 personal cases studied bioptically, that so-called "senile cirrhosis" is the terminal phase of liver sclerosis of various nature, difficult to differentiate from genuine cirrhosis.

Treatment of Intermittent Claudication with Vitamin E.

Livingstone, P. D., and Jones, C. *Lancet* **2:** 602 (Sept. 20) 1958.

Conflicting opinions as to the value of vitamin E in the treatment of peripheral vascular disease prompted a controlled study of its use in patients with intermittent claudication. Seventeen male patients with obliterative vascular disease and intermittent claudication, of average age 56 years, received 600 mg. daily for forty weeks. Seventeen control patients received a placebo during this double-blind study. The results were judged by the patients' own assessment of the medication and by improvement in results of an exercise tolerance test. Thirteen of the vitamin E group improved, whereas only 2 control patients showed improvement. These patients had undergone other forms of treatment with satisfactory results. The fact that improvement occurred only after several months makes it unlikely that psychologic factors could account for the benefit. Likewise, the duration of the symptoms for approximately five years in all patients makes it unlikely that the intermittent claudication disappeared spontaneously. It was not possible to select patients most likely to respond. It was confirmed that large doses of vitamin E and prolonged treatment are necessary. As a result of this study, it appears that in some cases of intermittent claudication, vitamin E does confer benefit.

A Means of Lowering Elevated Blood Cholesterol Levels in Patients with Previous Myocardial Infarction.

Meltzer, L. E.; Bockman, A. A., and Berryman, G. H. *Am. J. M. Sc.* **236:** 595 (Nov.) 1958.

The blood cholesterol levels of 28 hypercholesterolemic myocardial infarction patients were followed for six months during which an unsaturated fatty acid-sitosterol-pyridoxine-

vitamin E formula was added to their pre-existing diets. The 28 patients were grouped according to their previously standardized dietary fat intakes, namely, Group I consisted of 10 patients who received less than 50 Gm. of fat daily; Group II, made up of 8 patients who ingested 50 to 100 Gm. of fat daily; and Group III, 10 patients who took 100 to 150 Gm. of fat daily. The baseline cholesterol level for each patient had been well established by frequent analyses during a preliminary observation period of six to twelve months; in all cases it had remained persistently elevated. The value used was the lowest attained. Every subject showed a decrease in the baseline blood cholesterol level at the end of a three-month "treatment" period during which each received 4 tablespoonfuls of formula (each tablespoonful contained 300 mg. of plant sterols, 1.0 mg. of pyridoxine, and 9.8 Gm. of safflower oil which contained 20 mg. of vitamin E) daily with meals. The decrease was maintained (or additionally lowered) during a subsequent three-month "maintenance" period during which 2 tablespoonfuls of formula were given daily with meals. The over-all change at the end of six months was significant for all patients in Group I, and for 7 of 8 and 7 of 10 patients in Groups II and III, respectively. The magnitude of decrease appeared to be influenced by the amount of weight gain, but in no case was there an elevation over the original baseline level, even in the presence of a considerable gain in weight. The greatest decline in the blood cholesterol level was found in association with low and intermediate dietary fat intakes; in these cases, weight gain was slight or absent. (From authors' summary.)

A Word-Association Test of Emotional Disturbance in Older Women.

Olsen, I. A., and Elder, J. H. *J. Gerontol.* **13:** 305 (July) 1958.

Responses of a sample of normal women over 60 years of age to a word-association test were compared with those of a comparable sample of younger subjects, in order to determine the relative importance of certain sources of emotional disturbance. The areas investigated were "money," "general health," "specific somatic preoccupations," "aging and death," "religion," and "emotional reactions." The responses obtained were analyzed on the basis of reaction times and also by the content of the responses according to normal and disturbed categories. The results suggest that the "critical words" were indeed more disturbing to the older women. The areas "money," "emotional reactions," "aging and death," and "religion" proved to be the sources of greatest disturbance. Health factors, either "general health" or "specific somatic preoccupations," did not reveal important differences between the older and the younger subjects. These findings are suggestive of possible sources of emotional disturbances in women over 60 years of age who seem, at least on the more obvious levels, well adjusted and useful members of a community. (Authors' summary.)

Preliminary Report on the Effect of Triamcinolone (Aristocort) in Edematous Patients.

Page, R. G., and Lavender, A. R. 31st Sci. Session, Am. Heart Assoc., October, 1958; Abstract, *Circulation* **18:** 764 (Oct.) 1958, Part 2.

Triamcinolone, a steroid with a 16-alpha-hydroxy group, has been reported to increase urinary sodium excretion in experimental animals as well as in patients who were being treated for a variety of diseases. The present study was undertaken to determine the effect of this steroid in edematous patients. Several (1 nephrotic and the rest cardiac) were given triamcinolone in doses ranging from 4 mg. to 64 mg. per day for different lengths of time. Urinary sodium, potassium and chloride were determined daily. Daily weights were determined when possible. Serum electrolytes were measured at different intervals. There were no significant changes in serum values. The urinary response was variable. The most "beneficial" effect was seen in a patient in whom there was an increased secretion of sodium and potassium during treatment, and there was a continuation of the natruresis following the discontinuance of the drug. There was a concomitant increase in urinary sugar in this patient, a known diabetic. The increase in urinary electrolytes may have been secondary to this. In the majority of the patients there was a depression in urinary sodium output with

little change in the potassium values. There seemed to be some correlation between the dose and the degree of depression. Some patients showed a rebound phenomenon, that is, an increase in urinary sodium following discontinuation of the drug.

Comparison of Total Cholesterol Levels in Blood Serum with Lipid Concentrations in Human Coronary Arteries. A Second Interim Report.

Paterson, J. C., and Derrick, J. B. D. *Canad. J. Biochem. Physiol.* **35:** 869, 1957; Excerpta Med. (Gerontol. & Geriatrics) **1:** 74 (Aug.) 1958.

This report gives the results of a comparison of the levels of total serum cholesterol, determined serially during life in 88 patients, with the concentrations of total lipid extracted from large segments of the coronary arteries of the same patients after death and necropsy. No significant relationships were observed in persons between 60 and 89 years of age, whether the comparisons were made in the entire series of patients or in those of the same age group at the time of death. The data in younger persons were inadequate for statistical analysis. Terminal loss of weight from wasting disease processes bore no significant relationship to the concentration of lipid in the coronary arteries of the entire series of patients, or of those in the same age group. In general, the antemortem serum cholesterol levels of the 88 patients were found to be remarkably constant over periods of as long as four years.

Der diagnostische Wert intrakutaner Venektasien. (The Diagnostic Value of Intracutaneous Venectasies).

Rotzsh, W., and Woratz, G. *Ztschr. f. Alternsforsch.* **12:** 244 (Dec.) 1958.

Intracutaneous dilatation of the veins at three predilection points in the skin—the face, the costal bow, and the legs—were investigated in 1,000 patients without evidence of venous disease. All three skin areas showed pronounced signs of aging. A statistically significant correlation was found between intracutaneous and subcutaneous varices of the legs. The venous picture in the face was intensified by sunlight. Dilatation of the veins of the face and of the costal bow was significantly more frequent in men than in women. An unequivocal statistical correlation also was found between age and the progressive dilatation of the leg veins; the mean index for the veins of the legs was higher in women than in men. The authors believe that intracutaneous dilatations of the veins indicate a slight insufficiency of the circulatory system with advancing age, or that they are caused prematurely by various kinds of exertion which can be traced not only to causes proved statistically but perhaps to causes as yet unknown. (Authors' summary.)

A New Look at Pulmonary Embolectomy.

Steenburg, R. W.; Warren, R.; Wilson, R. E., and Rudolf, L. E. *Surg., Gynec. & Obst.* **107:** 214 (Aug.) 1958.

This is a report of the first successful embolectomy for massive pulmonary embolism performed in the United States. The patient was a 65-year-old woman in whom a pulmonary embolism developed on the sixth day following cholecystectomy and choledochostomy. All aspects of the case were favorable for the procedure; it was diagnosed promptly and the patient moved quickly to the operating room. Experience with the management of cardiac arrest and resuscitation was responsible for the survival of the patient. The interruption of a major vein to prevent a scond embolism was also performed. The Trendelenburg technic as modified by Meyer (1930) was used. A sternum-splitting incision or a transverse sternal approach would have furnished more rapid and better exposure than the parasternal approach used in this patient. Pulmonary embolectomy was abandoned in this country about 1940 because of the lack of success with it and because of the hope that the postoperative use of anticoagulants would make this operation unnecessary. This goal has not been

achieved and, therefore, patients without major complications who live long enough (fifteen minutes or more) so that a reasonably certain diagnosis can be made should be considered as candidates for operation. The major diagnostic points are distended neck veins, electrocardiographic findings of acute cor pulmonale, and the elimination of other diagnoses, particularly myocardial failure, massive sepsis, hemorrhage and acute electrolyte imbalance. The diagnostic steps should be taken with the patient already in the operating room. The operation should be undertaken without delay once the diagnosis is certain and the embolus is of a size to cause sustained circulatory embarrassment. All conditions being met, it is estimated that between 20 and 30 per cent of massive pulmonary emboli will prove amenable to surgery.

"Salicylate Anaemia."

Summerskill, W. H. J., and Alvarez, A. S. *Lancet* **2:** 925 (Nov. 1) 1958.

Severe "iron-deficiency" anemia, of uncertain cause despite extensive investigation, had required continuous treatment with iron for five years and ten years, respectively, in a man aged 47 and a woman aged 40 years. Laparotomy had been advocated in both patients, and total hysterectomy had failed to influence the anemia in the woman. Habitually heavy consumption of salicylate compounds for headaches had coincided with the onset and subsequent course of the anemia in both patients. Occult bleeding from the gastro-intestinal tract was demonstrated during controlled periods of salicylate medication. After salicylate consumption had been greatly reduced, anemia did not recur during follow-up periods of thirteen and ten months without iron therapy. Salicylate consumption is proposed as a possible cause of anemia. (From authors' summary.)

Sulfaphenazol (Orisul) in Urology.

Susset, J. G. *Canad. M. A. J.* **79:** 992 (Dec. 15) 1958.

Sulfaphenazol (3-sulfanilamido-2-phenylpyrazol) was used prophylactically in 42 patients and therapeutically in 58 patients with urinary-tract infections. Of the entire group, 96 had undergone operations on the urinary tract, 3 had chronic prostatitis, and 1 chronic cystitis. The dosage was 2 Gm. orally in fractional doses for two days followed by 1.5 Gm. for the next five days. Protection against infection was achieved in 93 per cent of the prophylactic group—a good record in view of the large number of patients with indwelling catheters or undergoing repeated diagnostic procedures. The drug eradicated urinary-tract infection in 77 per cent of the patients with such an infection. No change occurred in 9 (16 per cent), and 4 (7 per cent) had increased pyuria. These patients all had severe infections. In prostatitis, the number of pus cells in the prostatic smear after treatment decreased. The patient with chronic cystitis improved. No toxic manifestations, evidence of renal damage, or hypersensitivity reactions occurred. No incipient symptoms of neuritis were observed even though the series included many elderly patients. Sulfaphenazol has the advantage of low dosage and seems to be inferior in no way to sulfonamides currently in use.

Klinische Erfahrungen mit Viomycin (Vionactan-Pantothenat). (Clinical Experience with Viomycin (Vionactane-Pantothenate).)

Tanner, E., and Merian, P. In: Neue Tuberkulostatika und Tuberkulostatika-Resistenze von Tuberkelbacterien. Symposium at University Medical Clinic, Freiburg, February 10 and 11, 1958. Ed.: A. M. Walter; (Tuberkulosearzt Monogr. "Tuberkulose-Bücherei") Stuttgart 1958, p. 64; through Ciba Literature Review **3:** 335, 1958.

Tuberculosis patients, in whose sputum sensitive bacteria could be detected, were divided upon admission into two random groups. The first group was given streptomycin,

isonicotinic acid hydrazide (I.N.H.), and p-aminosalicylic acid (P.A.S.), whereas the other received Vionactane P, I.N.H., and P.A.S. Only those patients in whom medical treatment was continued without interruption for at least three months were included in the evaluation. Each group contained 46 patients with equally severe disease, roughly 25 per cent being old cases. The average total dosages of Vionactane P and streptomycin were 70 Gm. and 38 Gm., respectively. The general condition, temperature, weight, cough, and amount of sputum were beneficially affected. Four-fifths of the patients showed radiographic improvement. Freedom from bacilli was obtained with Vionactane P after an average of 2.5 months in 78 per cent of cases, and with streptomycin after 2.9 months in 75 per cent. Both antibiotics brought about good regression in infiltrations. Closure of cavities was somewhat more frequent in response to streptomycin. Nineteen other patients with tuberculosis, who could no longer be given other tuberculostatic agents because of resistance or intolerance, received Vionactane P combined with streptomycin and I.N.H., or with pyrazinamide. Vionactane always proved effective in these patients. Vionactane P was, as a rule, well tolerated. Hyaline casts or protein were sometimes excreted in the urine, and retention of urea developed in 2 patients. Induration at the site of injection occurred in 3 patients.

A New Diagnostic Procedure for Mild Diabetes Mellitus. Evaluation of an Intravenous Tolbutamide Response Test.

Unger, R. H., and Madison, L. L. *Diabetes* **7:** 455 (Nov.–Dec.) 1958.

An intravenous tolbutamide response test qualifies as a diagnostic test for diabetes. It has clearly differentiated diabetic and nondiabetic subjects in 95 per cent of tests. Performed in 70 diabetic patients and 100 nondiabetic control subjects, highly significant differences in the blood glucose response of the two groups were observed. The blood glucose concentration in diabetic subjects declined gradually following the injection of tolbutamide, but that in nondiabetic subjects fell sharply to a low point between twenty and forty minutes following the injection. The maximal separation of the groups occurred at twenty and thirty minutes. At twenty minutes, the blood glucose level of 94 per cent of diabetic patients remained at 84 per cent or more of the pre-test value. In 96 per cent of nondiabetic subjects, the level had fallen to 80 per cent or less of the pre-test value. Therefore, these levels were arbitrarily selected as the standards by which to interpret the test. The zone between 80 and 84 is nondiagnostic but should raise the suspicion of abnormality. This test has the advantage that it can be completed in thirty minutes and that it requires only 3 blood specimens. It has not as yet been evaluated in the presence of liver disease, endocrinopathies, infection or carbohydrate restriction. No untoward effects have occurred but caution is advised in using the test in patients with arteriosclerosis.

The Vitreous Gross and Microscopic Observations Seen in Age and Disease with Special Emphasis on the Role of the Vitreous in Detachment of the Retina.

Wadsworth, J. A. C. *Arch. Ophthalmol.* **58:** 455, 1957; Excerpta Med. (Gerontol. & Geriatrics) **1:** 103 (Aug.) 1958.

Gross and microscopic observations on a series of normal and pathologic eyes indicate certain patterns of change occurring with age and in the presence of disease. The changes are described and related particularly to the mechanism of retinal detachment. It is postulated that tears in the retina may be the result of senescent shrinkage of vitreous in the presence of retinal vitreous adhesions. Small secondary holes in the retina may be secondary to the pushing forward of the retina by the serous fluid behind it. The author does not believe that the peripheral cysts frequently described in the retina are a common cause of retinal detachment. Disinsertion of the retina results in detachment of the retina when the vitreous protrudes through the disinsertion, partially filling the subretinal space. He points

out that vitreous hemorrhage associated with age and disease may clear rapidly and may subsequently lead to retinal detachment. The nature of the subretinal fluid could be a helpful diagnostic aid. In the presence of serous detachments, subretinal fluid remains liquid and does not coagulate on fixation. In the presence of a choroidal tumor, on the other hand, the subretinal fluid is high in protein and quickly coagulates on fixation.

Black Cancerous and Noncancerous Lesions of the Skin.

Winkler, M. A. *Rhode Island M. J.* **41:** 490 (Sept.) 1958.

Senile keratosis: This disease occurs in areas exposed to the sun and especially where the skin shows microscopic or macroscopic evidence of senile degeneration. The lesion is irregular in contour with firmly adherent scales that are usually dull red or black. The black lesions contain increased melanin in the basal cells. Early lesions are level with the skin, whereas mature ones are more infiltrated and elevated. If a malignant change to squamous-cell carcinoma has taken place, the necrotic ulcerated surface will show a reddish-orange fluorescence under the Wood light. Histologically, the squamous cells will show anaplastic tendencies as seen in squamous-cell carcinoma Grade I, but to a lesser degree. Fulguration is the treatment of choice for senile keratosis but good results can be obtained with x-ray, radium, and excision.

Seborrheic keratosis: These lesions have a predilection for the trunk and show little tendency for malignant degeneration. They are commonly brown, but may be black. The original velvety surface may become waxy and verruciform. The epithelium shows hyperplasia with interweaving tracts of basal cells surrounding islands of connective tissue. Treatment consists of superficial fulguration.

Granulosa pyogenicum: These tumors resulting from trauma and infection show active granulation tissue, pronounced vascularity and rapid growth. When black bloody crusts form, they may resemble a malignant melanoma. Histologically, there are numerous capillaries embedded in edematous connective tissue, with a secondary inflammatory reaction that is absent in early lesions. Fulguration is the preferred treatment.

Basal-cell epithelioma: This relatively benign carcinoma of the skin is usually slightly darker than the skin but may be black. It shows little tendency to metastasis but it may undergo ulceration and peripheral extension by the formation of pearly rounded satellite lesions. Histologically, the mass of basal cells show basophilic nuclei, little protoplasm, and the loss of intercellular bridges. Treatment must be individualized and may consist of x-ray, radium, excision, or fulguration alone or in various combinations.

Black moles: These originally non-elevated congenital tumors may begin to project from the skin at puberty. They may be smooth, corrugated or multilobulated, soft or hard, and exhibit varying degrees of blackness. Histologically, they belong to the junction (active) nevi. Black moles may be transformed spontaneously or through trauma into malignant melanomas. Therefore, any change in a mole, such as scaling, purulent or sanguinous discharge, bleeding episodes, ulceration, or deepening of pigmentation should be cause for concern. Lesions that may simulate a black mole include sebaceous cyst, steatoma, hemorrhagic epidermic vesicle, traumatic tattoo, verruca vulgaris, nevus verrucosus, some tieche nevi, and a strangulated skin tag. Black moles are treated by excision.

Malignant moles: These lesions metastasize more frequently and more rapidly than other malignant growths. Histologically, the criteria for malignancy are 1) invasion of tumor cells into the upper layer of the epidermis, 2) the presence of ulceration, 3) the presence of mitotic figures, and 4) the presence of inflammatory infiltrate.

The Postoperative Psychoses.

Zeitlyn, B. B.; Stengel, E., and Rayner, E. *J. Ment. Sci.* **108:** 389, 1958, and *Proc. Roy. Soc. Med.* **51:** 937 (Nov.) 1958.

Postoperative psychoses, that is, mental illnesses that follow surgical operations, have received little attention from psychiatrists, and textbooks either do not mention them or

consider them along with the delirious or toxic exhaustive states. A group of 80 patients with reactions to operation severe enough to require admission to a psychiatric hospital were studied. In none was a postanesthetic syndrome observed. The type of reaction was affective in 46 patients, schizophrenic in 12, confusional in 21, and neurotic in 1. In the confusional category, only the cases associated with dementia or heart failure occurred immediately after surgery; in the majority the latent interval was six to fourteen days. No consistent response to successive operations was noted. Sex did not appear to influence the proneness to mental illness after operation, and there was no difference between the male: female ratio in postoperative psychoses and in psychoses generally. However, women were found to be more liable to this complication with increasing age. No evidence suggested that abdominal or gynecologic operations were more likely than others to be followed by psychosis, but hysterectomy appeared to carry a greater risk than other gynecologic operations. Among the possible explanations, the age factor seemed to be important. The incidence of the various psychiatric reaction types in the series matched that found in an observation ward; as an exception, the frequency of schizophrenia was significantly less than would be expected from the trend of psychoses generally. It is concluded that there is no evidence for the existence of an entity, "postoperative psychosis." Whether a psychosis occurs and what type, depends upon predisposing factors; the operation acts as the precipitating cause. The role of emotional factors remains uncertain. The patient probably would not have had the psychosis without the operation, but probably would have had it at some other time, precipitated by some other stressful event.

NEWS AND NOTICES

DUKE UNIVERSITY CENTER FOR THE STUDY OF AGING

The Duke University Center for the Study of Aging, Durham, N. C., has been awarded a grant of $200,000 to support over a period of approximately four years research on the socio-economic problems and potentials of older people. This research will be carried out under the direction of a small faculty committee composed of Professor John C. McKinney, Chairman of the Department of Sociology and Anthropology; Professor Frank de Vyver, Chairman of the Department of Economics; Dr. Paul Gross, Vice President of the University; Dr. Ewald W. Busse, Director of the Center for the Study of Aging; Dr. Alan C. Kerchkoff, Sociologist; Dr. Lloyd Saville, Economist; and Dean Alan K. Manchester. The research plans envision an investigation of the social and economic factors which limit the opportunities of the aged for employment and useful activity and will be focused on three general areas: one, relating to work and retirement; another, relating to family relationships and retirement; and finally, the inter-relationships between these two areas.

GERONTOLOGICAL RESEARCH FOUNDATION ANNUAL ESSAY CONTEST

The Gerontological Research Foundation offers two awards in its Annual Essay Contest: one to students in biology and medicine, and the other to students in the social sciences and social welfare. The awards will be made for recent research studies, particularly when there is evidence of original thinking on the part of the writer.

The awards are for $100 each and will be presented at the Twelfth Annual Meeting of the Gerontological Society to be held in Detroit, Michigan, November 12, 13, 14, 1959. Travel expenses will be provided for the winners.

Essays should not exceed 1500 words and should be submitted in triplicate no later than *August 1, 1959*. Manuscripts should be sent to: Scientific Director, Gerontological Research Foundation, 5600 Arsenal Street, St. Louis 9, Missouri.